EVALUATION OF SERUM FERRITIN AS A PROGNOSTIC MARKER IN ACUTE HEMORRHAGIC STROKE.

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CERTIFICATE

This is to certify that the dissertation entitled "**EVALUATION OF SERUM FERRITIN AS A PROGNOSTIC MARKER IN ACUTE HEMORRHAGIC STROKE "** is a bonafide work done **Dr.R.SOWRI RAJAN @ GOVINDARAJ**, at Madras Medical College, Chennai in partial fulfillment of the university rules and regulations for award of M.D., Degree in General Medicine (Branch-I) under my guidance and supervision during the academic year 2010 -2013.

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I solemnly declare that this dissertation entitled "**EVALUATION OF SERUM FERRITIN AS A PROGNOSTIC MARKER IN ACUTE HEMORRHAGIC STROKE"** was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, during 2010-2013 under the guidance and supervision of **Prof.E.DHANDAPANI, M.D.** This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine (Branch-I).

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INTRODUCTION

Cerebrovascular disease is arguably most devastating of the neurological disease affecting mankind. The term stroke or apoplexy (Gr.being struck down) is applied to sudden focal neurological syndrome, specifically the type caused by cerebrovascular disease.

Intracerebral hemorrhage was first recorded by the Swiss physician Wepfer (1620–95) and in more detail by Morgagni (1682–1771) in Padua. Nonhaemorrhagic stroke, 'serous apoplexy', greatly puzzled the medical community until cerebral softening ('*ramollissement'*) was recognized as a pathological entity in 1820 by Rostan (1790–1866) in Paris. Initially it was regarded as an inflammatory condition. The term 'infarction' was coined by Cohnheim, one of Virchow's disciples.A landmark in the recognition of the anatomical substrate of the stroke was the work of Morgagni (1682-1771) Professor of medicine and subsequently of pathological anatomy in Padua. In 1761 , Morgagni published a impressive series of clinicopathalogical observation collected over his lifetime at the age of 72. Morgagni not only confirmed the notion of crossed paralysis , but also firmly divided apoplexy into sanguineous apoplexy and serous apoplexy (1). Portal (1742-1832) rightly emphasized that it was impossible to distinguish between the two during life (2).

The cerebrovascular disease include the following principle categories,1.Infarction –through occlusion of major arteries , small arteries or venous sinuses,2.Hemorrhage – most often through rupture of small arteries, arterioles, aneurysms or capillaries.

Strokes are common with annual incidence of 42-100/10000. It is the second most common cause of death in Europe and heart failure. It is the third most common cause of death after heart failure and cancer in united states. Overall it is the second most common cause of death worldwide (3).

Stroke Morbidity and Mortality in India

Prevalence 55.6 per 100,000 all ages (4);0.63 Million deaths (5) ;1.44-1.64;million cases of new acute strokes every year (6.);6,398,000 DALYs (7.).12% of strokes occur in the population aged <40 years (8).28-30 day case fatality ranges from 18-41% (9, 10,11)

The consequence of stroke is devastating. Apart from the functions specific to the lost brain tissue, other essential mental faculties such as humor, mood, initiative, and speed of thought are severely affected. Sadly these attributes are ignored in the treatment of stroke patients.

AIMS OF THE STUDY.

1. To find the serum ferritin levels in patients with intracerebral hemorrhage.

2. To find the serum ferritin level between different prognostic groups.

3.To assess the correlation between serum ferritin level and severity of acute intra cerebral hemorrhage.

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REVIEW OF LITERATURE

HEMOGLOBIN

Hemoglobin contains heme, a cyclic tetrapyrole consisting of four molecules of pyrole linked by alpha methylene bridges. This planar network of conjugated double bonds absorbs visible light and colors heme bright red (12).

One atom of ferrous iron Fe2+ resides at the centre of the planar tetrapyrole. Oxidation and reduction of Fe and Cu in the cytochromes is essential to their biological function as carriers of electrons. By contrast, oxidation of Fe 2+ of hemoglobin and myoglobin to Fe3+ destroys their biological activity. They oxygenate instead of oxidizing (12).

FREE RADICAL INJURY.

Peroxidation of lipids when exposed to oxygen is responsible for damage to the tissues in vivo. This deleterious effects are caused by free radicals ROO*,RO*,OH* produced during peroxide formation from fatty acids. Lipid peroxidation is a chain reaction providing a continuous supply of free radicals that initiate further peroxidation (13).

(1*) INITIATION*.

$$ROOH + METAL\ (^{n}) \rightarrow ROO^{*} + METAL\ (^{N-1}) + H^{*}$$

$$X^{*} + RH \rightarrow R^{*} + XH$$

(2).*PROPAGATION*.

$$R^{*} + O_2 \rightarrow ROO^{*}$$

$$ROO^{*} + RH \rightarrow ROOH + R^{*}$$

(3).*TERMINATION*.

$$ROO^{*} + ROO^{*} \rightarrow ROOR + O_2$$

$$ROO^{*} + R^{*} \rightarrow ROOR$$

$$R^{*} + R^{*} \rightarrow RR$$

Lipid peroxidation is a chain reaction with potentially devastating effects. To control and reduce peroxidation, humans have antioxidants. Chain breaking antioxidants are glutathione peroxidases that react with ROOH. In vivo the principle chain breaking antioxidants are Superoxide dismutase which act in the aqueous phase to trap superoxide free radicals 02-.Urate and Vitamin E act in the lipid phase to trap ROO* radicals.

FREE RADICALS.

Molecules or molecular fragments which have one or more unpaired electrons are called free radicals (14). Any chemical moiety containing an oxygen atom with an unpaired electron in the outer orbital shell is called an oxygen free radical. Univalent reduction of oxygen or the action of ionizing radiation of oxygen results in the formation of oxygen free radical.

Potentially cytotoxic reactive oxygen species are,

O_2^- - SUPEROXIDE	OH* - HYDROXY RADICAL
HO_2* - HYDROPEROXYL	ROO* - PEROXIDE
H_2O_2 - HYDROGEN PEROXIDE	O^- - SINGLET OXYGEN.

In the normal system, 2% of oxygen free radicals are produced by mitochondria due to inadequate utilization of oxygen. This may be produced more when the efficient functioning of electron transport is compromised (15).

Free radicals may react with membrane lipids by lipid peroxidation. Each lipid peroxide that is produced is itself a free radical and once produced, triggers a autocatalytic process as each lipid attack neighboring fatty acid to yield additional lipid peroxide products (16 , 17).

BRAIN AS A TARGET OF FREE RADICAL INJURY.

Brain is especially vulnerable to the free radical injury because of high content of unsaturated fatty acids and relative deficiency of antioxidant mechanisms. Unsatturated fatty acids account for more than 20% of fatty acids in the body (18).Human brain has only 3% of total glutathione peroxidase of liver, completely devoid of non selenium containing enzymes. Catalase levels are only less than 1 % of liver and RBC. The vitamin E levels are also less than 50 % of that of liver. On the other hand brain contains high levels of ascorbic acid (19).

IRON AND THE FREE RADICALS.

In general iron in the human serum is bound to proteins in hemoglobin and myoglobin. About 2/3rd of body iron is in the form of hemoglobin. To participate in free radical formation, iron must be liberated from the protein (18). The liberated iron catalyses the formation of free radicals by two reactions, 1. Haber Weiss reaction and 2. Fentons reaction.

Haber Weiss reaction.

Reaction of superoxide with hydrogen peroxide to produce highly reactive hydroxyl radical in the presence of iron (20).

$$O_2^- + H_2O_2 \rightarrow O_2 + OH^- + OH^*$$

Fenton's reaction

Hydrogen peroxide in the presence of ferrous iron produces highly reactive hydroxyl radical (21).

$$H_2O_2 + Fe^{2+} \rightarrow Fe^{3+} + OH^* + OH.$$

Further more studies have shown that the catalyses of hydroxyl radical formation from the hydrogen peroxide requires Fe^{2+}, and Fe^{3+} being ineffective (22). When iron forms complexes with di and triphoshate ester nucleotides ,Fe^{2+} remains in a catalytically active state. Thus if iron is available for movement in to the cell, it may ligate with the di and triphosphate esters and is easily reduced by ascorbate to the ferrous form which is very effective in catalyzing hydroxyl formation from hydrogen peroxide (23).

In a large prospective study, Salonen & coworkers showed elevated serum ferritin consisted a strong risk factor for acute myocardial infarction . Stored iron in the form of ferritin is not essential for sustaining life or for preventing anemia, but when liberated, it can promote tissue injury by provoking iron mediated Fenton reaction (24).

The liberation of iron and heme compounds from hemoglobin following hematoma, hemorrhagic infarction, or head and spinal cord injury is a critical factor in the initiation of neuronal death (Braugher et al) (25). Ikeda et al 1989 showed the iron chelator deferoxamine to be protective against cold induced brain edema (26, 27). Hall and braugher showed that 21 amino steroids specifically developed to quench iron induced free radical induction, ameliorated spinal cord and brain edema due to trauma.

IRON METABOLISM

The iron absorption takes place largely in the proximal small intestine and is a carefully regulated process. For absorption, iron must be taken by the luminal cell. This process is facilitated by the acidic content of the stomach which maintains the iron in solution (28). At the brush border of the absorptive cell, the ferric iron is converted into ferrous iron by ferrireductase. Transport across the membrane is carried by divalent metal transporter (DMT 1).DMT1 is a general cation transporter. Once inside the gut cell, iron can be stored as ferritin or transported throughout the cell to be released at the basolateral

surface to plasma transferrin through membrane embedded iron exporter called ferroportin (29).

The function of ferroportin is negatively regulated by hepcidin, the principle iron regulating hormone (30). In the process of release, iron regulates with another ferrroxidase called hepahastin, which oxidizes the iron to the ferric form for transferrin binding. Once the iron bearing transferrin interacts with the receptor, the complex is internalized via clathrin coated pits and transported to an acidic endosome, where the iron is released at the low pH. The iron is made available for heme synthesis while transferrin receptor complex is recycled to the surface of the cell.

SERUM FERRITIN:

Free iron is toxic to cells and the body has established an elaborate set of protective mechanisms to bind iron in various tissue compartments. Within cells iron is stored complexed to protein as ferritin or hemosiderin.Apoferritin binds to free ferrous iron and stores it in the ferric state .As protein accumulates within the cells, protein aggregates are formed called hemosiderin (31).

Under steady state concentrations, the serum ferritin levels correlate with the body iron stores. Thus the serum ferritin level is the most convenient laboratory method to estimate iron stores (32).

Adult males have serum ferritin values averaging 100mcg/l, while adult females have 30 mcg/l.

As the iron stores are depleting, the serum ferritin levels fall less than 15mcg/l. Such levels are diagnostic of absent iron stores.

Ferritin is the key storage protein in the brain. Fully assembled ferritin contains 24 subunits of H and L chains. The H chain has ferroxidase activity and can convert ferrous iron to ferric iron thereby limiting the availability of ferrous iron to participate in the production of free radicals (33,34).

IRON STORE	**MARROW IRONSTAIN**	**Sr.FERRITIN (mcg/l)**
0	0	Less than 15
1-300mg	Trace to 1+	15 -30
300-800	2+	30-60
800 – 1000	3+	60 -150
1-2g	4+	More than 150
Iron overload	-	>500-1000.

IRON AND VASCULAR DISEASE

In 1981, JL Sullivan proposed the iron hypothesis, stating that increased incidence of coronary disease in men and postmenopausal women is due to

increased body iron stores (35). Grobbee .et al. in a population based cohort study of 11,471 Dutch postmenopausal women concluded that higher serum ferritin concentrations in postmenopausal women are associated with increased risk of ischemic stroke (36). Iron plays a critical role in atherosclerosis by oxidizing LDL to form oxidized LDL which is highly atherogenic. It can also activate platelets via protein kinase C mechanism (37).

The role of iron in cardiovascular disease and carotid atherosclerosis has been proved by many independent investigations. In study of health in Pomerania SHIP, Birger wolf et al identified a relationship between serum ferritin levels and carotid atherosclerosis which was potentiated by LDL (38).

Iron and CVA.

Iron induced brain damage has been extensively studied by A.Davlos et al. They showed elevated serum ferritin measured at the onset of symptoms increased the risk of progression to stroke by 33% , independent of other predictors of neurological outcome (39 ,40).They demonstrated that serum ferritin levels are stable during the 72 hours after the acute stroke and are unrelated to the other biochemical markers of stress reaction (41) and the relation between plasma ferritin and progressing stroke was independent of the ultimate infarct volume. So increased ferritin values predict early neurological worsening also in small cerebral infarcts.Blood ferritin is a reliable indicator of tissue iron and therefore might be a suitable index of availability of iron in the

infracted area of acute stroke patients without infectious or inflammatory disease.Comparatively serum iron and transferrin saturation have a high analytic variability due to hemolysis and extensive day today variability (30 – 50 %) (42,43)

Coyle et al and others in various experimental works showed an interaction between iron and glutamate release and free radical injury and subsequent neuronal death. Intra ischemic glutamate release in penumbra cortex correlates positively with enhanced free radical activity during reperfusion after transient middle cerebral artery occlusion (44).

Huan Dong et al from Southern medical university, China studied the expression of H chain of ferritin in brain samples from 19 patients undergoing surgery for traumatic brain injury by RT-PCR, immunohistochemistry and Western blot.

They found that iron was overloaded and ferritin H chain was upregulated in human cortex after TBI. The enhanced expression of ferritin remained elevated for a long time till 48^{th} hour post injury. Experimental evidence also suggests that HO-1 was upregulated and the increased HO-1 can accelerate heme degradation and can set in a vicious circle. Inhibition of HO-1 has been associated with attenuation of perihematomal edema volume in ICH (45).

Serum ferritin and perihematomal edema volume.

Among other factors of morbidity and mortality in ICH, perihematomal edema volume also plays a significant role. In ICH the edema occurs in two phases. In the early phase, edema is due to the hydrostatic pressure of hematoma formation and clot retraction.The delayed phase is due to the hemolysis and neuronal toxicity in part mediated by iron.

In a retrospectively reviewed and prospectively collected clinical and laboratory data from 23 consecutive patients with acute spontaneous ICH, Manu Mehdiratta et al showed that delayed iron toxicity played a role in causing brain injury and edema formation after ICH (46).

Xi.G.et al infused lysed erythrocytes into the rat brain and found out marked edema formation within 24 hours. However when they infused packed cells, edema peaked on day 3 coinciding with the RBC lysis and release of Hb (47,48).

Savman et al. compared the level of non protein bound iron (NPBI) in the CSF of 20 preterm infants with intraventricular hemorrhage and 10 preterm control infants. They found out NPBI in 75% of the patients with IVH and 0% in control infants. The NPBI was found in very high levels in CSF from patients with IVH and also in those with white matter lesions and subsequent disabilities (49).

Manu Mehdiratta found little correlation between change in hematoma volume and corresponding relative edema volume between admission and day 3.They concluded that perihematoma edema formation cannot be solely considered an epiphenomenon of hematoma growth (46).

Serum ferritin might be the suitable indicator of the availability of iron and ferritin in the area of ICH. After ICH when the blood leaks out of the blood vessels, ferritin at the hemorrhage site is partly derived from the serum as the blood serum separates from the clotted blood following clot retraction, thereby releasing its ferritin into the hematoma site. There is also indirect evidence to suggest that iron released from the lysed RBCs is likely influenced by serum ferritin levels.

Natalia Perez et al studied 92 consecutive patients with primary hemispheric ICH. They determined serum ferritin levels and other inflammatory markers. They found out 51 (55%) patients had poor outcome (Rankin score >2).Advanced age, high stroke scores, large hematoma volume, intraventricular extension, mass effect and high ferritin values at baseline were associated with poor outcome. The higher the ferritin quartile, the worse the Rankin scores. Ferritin levels remained stable for 72 hrs and did not correlate with acute phase reactants. They concluded that high ferrritn levels at admission are independently associated with poor outcome in patients with ICH and suggested

the neurotoxic effect of increased body iron stores in patients with hemorrhagic stroke (49).

Serum ferritin as an acute phase reactant.

Arola Armengou et al studied a group of 34 consecutive patients with an acute ischemic stroke of <8 hours duration. They collected blood samples at admission, 24 hrs, 48 hrs, and day 5 from symptom onset. They measured serum ferritin, cortisol, CRP, leucocyte count and plasma fibrinogen. Their study showed no statistical difference between the concentrations of ferritin at admission and those obtained before 48 hours. Whereas cortisol values increased significantly and CRP showed moderate increase after 24 hours. They confirmed serum ferritin concentrations are not associated with stress reaction and acute phase reactants in patients with stroke.

The nonsignificant rise in serum ferritin during the first 2 days after stroke is of insufficient magnitude to explain the large difference in ferritin levels between the patient with good prognoses and those with bad prognoses (50).

In a comparative study of serum ferritin and the acute phase reactants in patients undergoing minor and major surgery, M.F Asalou et al, showed the ferritin levels rises only after 3 days of the inciting stress. The levels remain stable before 3 days of the surgery (51).

INTRACEREBRAL HEMORRHAGE

Bleeding into the substance of the brain was recognized as a cause of stroke by Morgagni in1761. Cheyne wrote a treatise on apoplexy and coma in 1812, in which he included examples of intracerebral hemorrhage (52).

INCIDENCE AND EPIDEMIOLOGY

Approximately 10% of strokes are caused by ICH.(53,54,55) .Populations with high prevalence of hypertension such as Asians and African Americans have a higher incidence of ICH. ICH affects a wide age range, with many examples in the seventh, eighth, and ninth decades of life. Higher percentage of strokes in patients younger than 40 years are hemorrhagic, and ICH is also common during the later years of life.

PATHOGENESIS

In the study conducted on autopsy specimen by Fisher (56), the hematoma contained a central mass of clotted blood surrounded by fibrin caps called globes. It represented the fibrin caps of small ruptured blood vessels surrounding the hematoma.

After ICH, as the hematoma expands, the surrounding small blood vessels break resulting in expansion of the hematoma. Slowly the hematoma grows like a snow ball. The intracranial pressure slowly rises and the tissue pressure

surrounding the hematoma also rises. Thus a new equilibrium is reached, bleeding stops and the hematoma stops growing. If the hematoma reaches the surface of ventricle it may decompress itself into CSF.

SYMPTOMS

The symptoms of hemorrhage into the brain develop gradually because the blood is usually from small vessels and is released under capillary pressure. In contrast to SAH, ICH develops gradually during minutes or sometimes hours.

In larger lesions, there is a smooth gradual worsening of function followed by vomiting and headache. Some patients may develop further detoriation after two days of initial stabilization .It is due to development of edema around the hematoma. When a detailed history is possible, nearly all patients with ICH have had a gradual evolution of symptoms and signs some more rapidly evolving than others (57).

Headache

As the brain parenchyma is pain insensitive, bleeding usually does not cause headaches. If the hematoma is near the surface of the brain as in case with lobar and cerebellar hemorrhage, the blood may irritate the meninges and cause headache and it may accompany meningeal signs (58).However headache is usually absent or minimal in small lesions. Patients with small, deep hematomas often never develop headache during their course of illness.(57).

Headache was not an invariable symptom in the 60 HSR patients with ICH. Headache was described in only 17 patients (28%) near the onset of

neurologic symptoms (59). Another seven patients (12%) noted headache later. Twenty-four patients (40%) had no headache at any time during their ICH. The 12 stuporous or comatose patients (20%) could not provide data regarding headache. Headache was much more frequent with larger lesions, and was often absent or minimal in patients with small lesions.

Decreased Level of Consciousness

Decreased level of consciousness has been found to be an important prognostic sign in nearly all series of ICH patients (60). Early reduction of consciousness is not an invariable accompaniment of ICH. When it occurs, however, it has an ominous prognosis. Loss of consciousness only occurs in patients with large hemorrhages and with brain stem involvement. It is either due to involvement of reticular activating system or due to increased intracranial pressure.

Vomiting

Vomiting is more common in ICH than any other cause of stroke and is an important sign. It is caused by increased intracranial pressure or due to distortion of 4^{th} ventricle as occurs in cerebellar hemorrhage. In posterior circulation hemorrhages, more than 50 % of the patients vomit. It reflects the involvement of vestibular nuclei or the vomiting center in the floor of the fourth ventricle (61). Patients with cerebellar hemorrhage almost always vomit early in their clinical course. In contrast, fewer patients with hemispheric infarcts vomit.

Seizures

Seizures are not common during the acute phase of a stroke, but are slightly more frequent in ICH than other stroke types, except embolism. Among three series of patients with spontaneous Nontraumatic ICH, 12.5%, 15.4%, and 17% of patients had seizures during their early course (62, 63,64).Lobar hemorrhages, slit-like hemorrhages situated near the gray-white junction of the cortex, and putaminal hemorrhages that undercut the cerebral cortex are especially epileptogenic (65).

Other Symptoms and Signs

Neck stiffness is found with caudate, thalamic, and cerebellar hemorrhages (66,67).Fever is relatively common, but is often related to infectious complications, such as pulmonary and urinary tract infections. Subhyaloid retinal hemorrhages, common in SAH, are rare in ICH, unless the hematoma has developed rapidly and is large (68). Cardiac arrhythmias and pulmonary edema develop in some patients with ICH, and are usually attributed to changes in ICP and catecholamine release, a similar pathogenesis to that used to explain cardiac findings in patients with SAH.

ETIOLOGIES

Hypertension

Hypertension is the most common cause of ICH. But there may not be malignant range of elevation in blood pressure. ICH may be the initial presentation of hypertension. In most patients presenting with ICH, it is difficult

to ascertain whether the elevated blood pressure is a due to Cushing response or the patient was hypertensive.

The occurrence of ICH in hypertension is biphasic, after developing considerable wear and tear on penetrating brain arteries, both during the early and late stages (69). During the early stages of systemic hypertension, the capillaries are exposed to the high pressure and consequently break and bleed. As the blood vessels are chronically exposed to increased blood pressure, degenerative changes develop in the vessel wall in the form of lipohyalinosis and milliary Charcot Boucher aneurysms. In the later stages, these degenerations cause arteriolar rupture and ICH.

Cole and Yates examined the brains of 100 hypertensive patients and 100 normotensive controls (70). All 13 patients with ICH had micro aneurysms and were hypertensive. Among 63 patients with microaneurysms, 46 patients had hypertension recognized during life. The age distribution of micro aneurysms was also interesting. Among 21 hypertensive patients younger than 50 years, only two patients had micro aneurysms, whereas 71% of hypertensive patients in the 65- to 69-year age range had microaneurysms.

Micro aneurysms are often surrounded by hemosiderin-laden macrophages, indicating previous leakage. The lesions are most common in penetrating arteries that supply the basal ganglia, thalamus, pons and cerebellum, and arteries supplying the gray-white matter cortical junctions of

the hemispheres. The same arteries that bear micro aneurysms also contain foci of lipohyalinosis and fibrinoid degeneration, which explains the dictum that ischemic lacunes have the same relative distribution as hypertensive ICH.

A relationship between iris aneurysms and cerebral micro aneurysms exists because rabbits with experimentally induced hypertension develop iris aneurysms approximately proportional to their development of cerebral microaneurysms (71).

Takebayashi et al in a study of surgical specimens of acute ICH showed that the penetrating arteries were the common site of bleeding but it had little relation to the micro aneurysms (72). Degenerative lipohyalinotic changes were present in the broken and adjacent arteries. Degenerative changes caused by aging and hypertension can predispose to ICH, but micro aneurysms may not often be the bleeding lesion.

Acute changes in the blood pressure without preexisting chronic hypertension can cause rupture of penetrating arteries and can predispose to ICH. In a clincopathalogical study of 218 patients, Bakemura estimated the prevalence of hypertension in patients died of ICH by using heart weight as an evidence of hypertension. He found out that only 46% of fatal ICH patients had evidence of moderate to severe hypertension and left ventricular hypertrophy. (73).

Brott and colleagues in a retrospective study of hospital records of patients with ICH admitted during 1 year period found out that only 45 % had

history of chronic hypertension. Another 12% without a history of hypertension had left ventricular hypertrophy. So they concluded that only 50 % of ICH can be attributed to chronic hypertension (74).However they found out that the locations of bleed was similar to that occurring in chronic hypertension. The hypertension recorded at the time of admission is probably an acute event which led to break down of unprotected capillaries and therefore was actually hypertensive hemorrhages. Another example of acute hypertension producing ICH is due to recreational drug usage like cocaine and methamphetamine which have strong symphathomimetic effects.

Patients have also developed ICH after sudden augmentation of cerebral blood flow, either locally to one hemisphere, as in the circumstance of ICH after carotid endarterectomy (75) or systemically, after correction of congenital heart defects or cardiac transplantation in the young (76,77). ICH has also been reported to develop during recovery from migraine. Intense vasoconstriction leads to diminished flow and, perhaps, ischemia to local blood vessels. Reperfusion then leads to ICH in the zone of prior vascular damage (78). A similar mechanism probably underlies most examples of hemorrhagic infarction caused by brain embolism.

The most common locations for hypertensive ICH in various series are: putamental-lateral ganglionic (25%-40%), thalamic (15%-30%), lobar (10%-30%), caudate (5%-10%), pontive (5%-10%), cerebellar (5%- 10%), and intraventricular (0% -5%). In postmortem analyses, an increasing number of

patients dying of lobar brain hemorrhages are found to have an unsuspected amyloid angiopathy.

Bleeding Diathesis

Coagulopathies whether acquired or inherited can predispose to intracerebral bleeding which is accentuated by hypertension. So far treatment with anticoagulation either with heparin or warfarin is the leading cause of ICH in patients with coagulopthy overall. .However it should be noted that ICH develops in only small number of patients who are on anticoagulation. Askey et al reported that in a series of 1626 patients on long-term anticoagulation only 30 had ICH, of which two thirds are fatal. The most important for ICH is the increasing prothrombin time beyond therapeutic range. Some hemorrhages occur even when the international normalized ratio is in the therapeutic range. As with other etiologies of ICH, hypertension aggravates the tendency to bleed intracranially(79).

Kase et al found three characteristic feature of anticoagulant induced bleeding. They are 1. Hemorrhage often develops gradually and insidiously during many hours, or even days;(6 of 14 patients with anticoagulant-related ICH in one series had an insidious clinical course). 2. The cerebellum and cerebral lobes are involved more frequently than in hypertensive ICH. 3. A high morbidity and mortality rate exist (15 of 24 patients died), and only patients with smaller hematomas (less than 30cc volume) had a favorable chance for survival; only 1 of 24 patients with ICH had bleeding elsewhere (80,81).

Treatment of anticoagulant-related ICH is a difficult task because most of the patients require anticoagulation as a prophylaxis against ischemic stroke. Patients with prosthetic heart valves, rheumatic mitral stenosis, or atrial fi brillation have a high risk for cerebral emboli without warfarin therapy. Because of their size and location in the surgically accessible cerebellum and cerebral lobes, many eventually require life-saving surgery. The initial clinical diagnosis may also be difficult in the group on warfarin for stroke prophylaxis because the first reaction to the neurologic symptoms is to predict that the patient had an ischemic stroke despite the treatment. The following general principles can be applied in ICH related to anticoagulation.

1. If a patient on anticoagulants develops neurologic symptoms, the cause is anticoagulant related hemorrhage until proven otherwise.

2. If anticoagulant hemorrhage is verified, immediately vitamin K, factor VIIa, or fresh frozen plasma should be administered. Aggressive measures should be taken to stop bleeding and the risk of embolism should not be a deterrent.

Although no formal prospective studies clarify the optimal time for restarting anticoagulants after ICH in patients who require long-term treatment, a retrospective analysis found that after 10 to 14 days, recurrent ICH did not develop (81). The decision on if and when to restart anticoagulants depends on the risk of embolization from the donor source (atrial fibrillation, prosthetic heart valves, etc.) and the risk of further intracranial bleeding. Studies seem to

show that the risk of embolization while anticoagulants are stopped is less than predicted and the risk of hemorrhage if anticoagulants are reintroduced is also less than expected. When the indication for anticoagulation is relative or questionable, it is probably best to discontinue anticoagulants, perhaps using platelet antiaggregants instead.

Leukemia, hemophilia, thrombocytopenia, von Willebrand disease, and disseminated intravascular coagulation are other important causes of ICH. Intracerebral hemorrhage can occur after thrombolysis for either ischemic stroke or myocardial infarction. The ICH developing in these settings is usually large and fatal (82).In this circumstance, hematomas usually begin within the region of brain infarction.

Drugs

Many abused substances are capable of causing stroke. It should be thought as a cause in young patients with ICH in whom other causes except trauma and arteriovenous malformations are less common. (83).

In amphetamine (speed), hemorrhages develop within few minutes of drug use. The most frequent presenting symptoms are headache, confusion, and seizures. Because of the coexistent edema and diffuse vasculopathy, there will be less focal signs inspite of large volume of bleed. When first examined by physicians, most patients with amphetamine hemorrhage do not have signs of sympathetic over activity, such as hypertension, tachycardia, or fever.

Citron et al studied 14 drug abusers, almost all admitting use of methamphetamine, among other drugs. At necropsy, a fibrinoid necrosis of the media and intima of small- and medium-sized arteries existed, resembling polyarteritis nodosa (84). Rumbaugh and colleagues studied the angiographic features of a group of methamphetamine abusers and noted beaded arteries with segmental constriction and dilatation of intracranial arteries. A potent solid form of d-methamphetamine base that can be smoked is now peddled in the streets (known as *ice*). This form is more potent and rapid acting. Angiography has often shown striking abnormalities in chronic amphetamine users and other patients with amphetamine-related ICH. Most common are segmental areas of constriction, irregularity, and occasionally fusiform dilatation. The focal vascular abnormalities usually emphasize superficial cortical arterial branches and are often referred to as *beading*. At times, the changes disappear on subsequent angiography. Unfortunately, these arteriographic changes have often been falsely attributed to arteritis. Beading and areas of vasoconstriction and dilatation is a non-specific sign and more often than not is not due to arteritis (85).

Cocaine is a potent narcotic that can be taken in many ways. Cocaine hydrochloride is usually snorted nasally. Cocaine hydrochloride is mixed with ammonia or baking soda to produce crack cocaine. It is precipitated as alkaloid cocaine after mixing with alkaline solution and is inhaled. Crack cocaine is absorbed quickly, reaching the brain in less than 10 seconds. Cocaine

hydrochloride can be taken in a variety of ways—orally, vaginally, rectally, sublingually, nasally, and by subcutaneous, intramuscular, or intravenous injection. Cardiovascular effects begin immediately after use and consist of an increase in pulse, blood pressure, temperature, and metabolism. The pressor effects of cocaine are similar to those of amphetamine and are probably mediated through a peripheral catecholamine mechanism.

The most common location of cocaine related ICH was lobar (57%). In others, the bleeding often involved deep structures known to be frequent sites of hypertensive ICH. In contrast to amphetamine related ICH, there is increased frequency of underlying vascular malformations in cocaine related ICH. Cocaine can cause extreme elevations of blood pressure and patient may develop cerebral edema and hypertensive encephalopathy in addition to ICH (86).

The other drugs that has a potential to cause ICH include phencyclidine PCP (angel dust), LSD and mescaline (87). They have sympathomimetic and vasoconstrictive properties but less implicated in causing ICH than cocaine and amphetamine. Other drugs causing ICH are Pentazocine and pyribenzamine (“T’s and blues”) or methylphenidate.

It is important to note that some over the counter medications that are sold as cold remedies are occasionally implicated in causing ICH.Phenyl propanolamine which has alpha adrenergic activity has been implicated in causing ICH among its users (88).The dose of PPA in weight control drugs was

higher than normally prescribed. In some patients there is an idiosyncratic reaction to the usual dose of PPA.Most often PPA related ICH occurs in patients taking it as over the counter drug for weight control. Very handful of cases is reported after taking cold remedies .So PPA has been removed from cold remedies in most of the countries. Angiographic changes similar to that of amphetamine has been described in long-term PPA users. Most of them cleared after abstinence for one month. (88).

Examples of putative PPA-related hemorrhages are difficult to evaluate. In some cases, use of diet pills was surely incidental, and in other patients, other multiple drugs and risk factors coexisted. In several patients, ICH occurred a few weeks postpartum, a time of vulnerability for spontaneous vascular complications. Although PPA has been shown to be associated with ICH in experimental animals and humans, reactions to PPA compounds are often idiosyncratic. A risk of ICH clearly exists for those who use PPA in a higher-than suggested dose. Prior hypertension; additional use of alcohol, coffee, or caffeine; concomitant use of monoamine oxidase inhibitors; and use during the postpartum period increase the risk of hemorrhage after PPA ingestion (89).

The phosphodiesterase inhibitors such as sildenafil, vardenafil and tadalafil were occasionally implicated in ICH.However it is difficult to evaluate whether the drug is causative or the increased blood pressure response that occurs during sexual intercourse caused the bleed (90).

Cerebral Amyloid Angiopathy

Congophilic or cerebral amyloid angiopathy (CAA) was recognized by Zenkevich as a potential cause of ICH, But Jellinger is probably most responsible for bringing this disorder to the attention of the neurologic community. There is a striking female prediliction. It has been recognized increasingly as a cause of ICH in elderly patients . Higher the age, higher the incidence of cerebral amyloid angiopathy (91).

It usually affects the small arterioles and arteries supplying the leptomeninges. The affected vessels show characteristic staining pattern with special stains. They stain positively with periodic acid Schiff and show acellular hyaline material. On staining with congored and when looked under polarized light, it shows characteristic apple green birefringence. The walls may seem duplicated or split. They are occasionally found in the cerebellum. Hemorrhages may be quite large and are often multiple. Some patients have recurrent ICH or SAH in different lobar sites, a finding in an elderly person that is virtually diagnostic of CAA (92).

In MRI imaging of the brain with echo planar technique, small scattered areas of old bleeds called micro bleeds are seen .These are predictive of future hemorrhages in CAA affected patients. Some patients may have Binswanger like picture showing diffuse white matter disease.

In older patients because of brain atrophy, the excess blood can be accommodated inside the cranial cavity without much increase in intra cranial pressure. So the symptoms are insidious without much head ache or vomiting.

Trauma

Trauma is one of the important causes not only in young but also in old age group. Often the history of trauma is not present or trivial. In some patients there may be retrograde amnesia to that event. In all patients, it is worthwhile to search for lacerations and bruises to find signs of trauma. Traumatic ICH is usually accompanied by contusions that are located in frontal and temporal poles as they hit upon the bony prominence. The contusions are often multiple. Occasionally hemorrhages may develop at the site of contusion after some period of time when the edema subsides. It is called spät hemorrhage (94).

SIGNS AND SYMPTOMS OF ICH AT COMMON LOCATIONS:

Keys to localization of ICH follow:

1. Motor signs—quadriparesis, hemiparesis, or no paresis
2. Pupillary function—asymmetry, size, and light reaction
3. Extra ocular movements—supranuclear, nuclear, internuclear gaze palsies
4. Gait abnormalities, especially ataxia

Hemorrhages of the Lateral Basal Ganglia, Putamen, and Internal Capsule

The hemorrhage caused by hypertension is usually located in the lateral portion of basal ganglionic capsular region. (94) As the bleed usually starts at the putamen, they are commonly called putaminal hemorrhages. The clinical features include contra lateral hemisensory loss, contralateral hemiplegia and ipsilateral deviation of eyes.

The hematoma may undercut the cortical connections, causing disconnection syndromes and result in transient cortical abnormalities. If the hemorrhage is in the left putamen, non fluent aphasia with preserved repetition occurs. Right sided lesions result in contralateral visual neglect, motor impersistance and constructional apraxia. However these abnormalities are transient and usually of smaller magnitude as compared to the cortical infarct or hemorrhage.

If hematoma is large, patient become stuporous. As the lesion enlarges there is increasing depth of coma and the ipsilateral pupil becomes constricted followed by dilatation. The ipsilateral plantar becomes extensor. Bilateral horizontal gaze palsy develops. Development of these signs carries grim prognosis. (95)

Caudate Hemorrhage:

Hemorrhage into the caudate nucleus accounts for approximately 7% of ICH. The blood discharges into the adjacent lateral ventricle resulting in its dilatation. So the signs and symptoms of increased intracranial tension develops earlier in caudate hemorrhages. The blood may track toward internal capsule or into the hypothalamus. The symptoms include headache, vomiting, depressed consciousness and neck stiffness. If the hematoma is large, there may be contralateral hemiparesis, conjugate deviation of eye towards same side with contralateral gaze palsy. Patient may develop ipsilatral miotic pupil with or

without Horners syndrome. There is minimal or absent symptoms and signs (96).

Thalamic Hemorrhage

In contrast to caudate or putaminal bleeds, there is very little motor paralysis in thalamic hemorrhage. It is because most of the pyramidal fibers are anterior to the hematoma and are spared or little affected. There are prominent sensory symptoms in the contralateral side of the body (97).

The key features of thalamic hemorrhage are the eye signs. The characteristic oculomotor abnormalities in patients with thalamic hematomas are as follows:

1. Paralysis of upward gaze, often with one or both eyes resting downward
2. Hyperconvergence of one or both eyes, with a combination of these findings giving patients the eyes inward at the tops of their noses
3. Ocular skewing, in which one eye rests below the other, with this divergence in vertical eye position remaining constant in gaze in all directions
4. Eyes gazing the wrong way resting toward the opposite side,
5. Disconjugate gaze, with limited abduction of one or both eyes (so-called pseudo sixth nerve paresis), failure of ocular abduction caused by visual fixation of the adducted eye, and increased convergence vectors neutralizing abduction-not caused by involvement of the sixth nerve.

These oculomotor abnormalities are caused by direct extension of the hematoma to the diencephalic mesencephalic junction or compression of the quadrigeminal plate region by the thalamic hematoma.

In thalamic hemorrhage, the pupils are usually small and react poorly to light because of interruption of the afferent limb of the pupillary reflex arc. Patients with large left thalamic hemorrhages often have an unusual aphasia (99). After beginning a conversation almost normally; patients may lapse into a remarkable fluent aphasia, with many jargon of nonexistent words and poor communication of ideas. In contrast to patients with Wernicke's aphasia, comprehension of spoken language is good.

Overall the prognosis is worse when compared to hemorrhages in other areas. Also the extension of the hematoma does not correlate with the mortality or morbidity. But the early occurrence of decreased alertness and increased sleepiness does not signify a poor prognosis as in other cases. It is due to the involvement of rostral reticular activating system.

Lobar Hemorrhages

Bleeding under the greywhite junction usually track along the white matter tracts .When the blood is absorbed , it results in a slit like shape giving the lesions the name "slit hemorrhage." Undercutting of the cortex can be epileptogenic, causing repeated focal seizures of limited duration (99). It is essential to diagnose subcortical bleeds because, the slit hemorrhage may be mistaken for infarct and antiplatelets may be erroneously prescribed. Due to its

superficial location, subcortical hemorrhages are accessible for surgical drainage. Most of the lobar hemorrhages are due to AVMs, CAA, or cavernous hemangiomas. Hypertension is also an important cause of lobar hematomas. The parietal and occipital lobes are affected more often than the frontal and parietal regions.

Symptoms and signs depend on the lobes affected, as follows:

1. ***Frontal hematomas***:

Far anterior lesions usually cause abulia. Patients appear apathetic and have reduced spontaneity, prolonged latency in responding, and short, terse replies. If the lesions extend deeply or toward the precentral gyrus, conjugate eye deviation toward the side of the hematoma and contralateral hemiparesis are found.

2. ***Paracentral hematomas:***

Lesions near the central sulcus produce contralateral motor and sensory signs, sometimes with aphasia if the lesion is in the left hemisphere.

3. ***Parietal hemorrhages:***

Parietal hemorrhages are usually accompanied by contralateral hemisensory loss, with neglect of the contralateral visual field. The limbs contralateral to the hemorrhage are often uncoordinated. Aphasia and disorders of reading, writing, and arithmetic functions are present when the lesions involve the left inferior parietal lobule. Patients with right inferior parietal

hematomas have defective drawing and copying and may have difficulty with visual spatial functions.

4. ***Occipital hematomas***:

Occipital hemorrhages cause a severe contralateral hemianopia, often with slight contralateral hemisensory or motor signs and visual neglect.

5. ***Temporal-lobe lesions:***

Temporal-lobe lesions often cause agitation and delirium. Wernicke type aphasia accompanies left temporal lesions. Temporal-lobe hematomas are particularly likely to swell and may cause herniation without preceding hemiparesis. Brainstem compression may develop insidiously, with deepening stupor. An ipsilaterally dilated pupil follows. Lobar hematomas are usually smaller in volume than deep lesions and have a lower mortality rate. The functional outcome in patients with lobar ICH is also generally better than other forms of ICH. The exception to good outcome is the occurrence of lobar hemorrhage in patients taking anticoagulants. Anticoagulant hemorrhages have a predilection for the cerebral lobes and the cerebellum, and often gradually increase in size. The diagnosis of lobar hemorrhage is often quite difficult without CT or MRI. Because of the higher incidence of vascular malformations and other bleeding lesions in patients with lobar hematomas, angiography is often indicated, especially in patients who are young and normotensive.

Primary Intraventricular Hemorrhages

Primary intraventricular hemorrhages are rare in adults. Hemorrhage into the ventricle occurs when an adjacent locus discharges the blood into the ventricular system. Caudate and thalamic hemorrhages are most common to discharge into the ventricles. (100).

In children most common cause of intraventricular hemorrhage is choroidal vascular malformations. As bleeding occurs the AVM are destroyed by themselves.

If the blood distends both the ventricles, symmetric hyper-reflexia and extensor plantar responses occur. Also at times, the bleeding is primarily into one lateral ventricle, and asymmetric focal signs may predominate. Decreased consciousness always occurs in IVH. The blood in the ventricular cavity can be aspirated using neurosurgical techniques.

Pontine Hemorrhage

Primary brainstem hemorrhages are located most often in the Pons. Midbrain and medullary hemorrhages are rare and when present, are usually caused by blood dyscrasias and vascular malformations.

Düret hemorrhages are pontine hemorrhages that are secondary to rapidly rising intracranial pressure. Raised ICP, especially if it develops quickly, frequently causes secondary lesions, so-called Düret hemorrhages. Primary Pontine hemorrhages usually begin in the center of the Pons at the tegmental-basal junction. These hematomas grow quickly and assume a round or oval shape, usually destroying the center of the tegmentum and base of the Pons.

Blood may dissect rostrally into the midbrain, but rarely extends caudally into the medulla. Hematomas frequently dissect into the fourth ventricle. Signs accompanying large medial pontine hematomas include (1) quadriparesis, often with limb stiffness and rigidity; (2) coma; (3) absent horizontal eye movements; (4) small but reactive pupils; and (5) rapid or irregular respirations. Vertical reflex eye movements are preserved unless the lesion extends rostrally into the midbrain. In some patients, the eyes spontaneously and repeatedly bob downward. Hyperthermia is sometimes noted.

Cerebellar Hemorrhages

Approximately 10% of ICH occurs in cerebellum. As it is a common site of hypertensive bleed, it is also a common site of anticoagulant related bleed. A study series by Toyada et al of 327 patients with ICH, 38 patients (12%) had their hemorrhage located in the cerebellum. Among them 75% were due to warfarin therapy. (101).

The site of bleed is usually the dentate nucleus due to rupture of distal branches of posterior inferior cerebellar artery and superior cerebellar artery. The involvement of brainstem is distinctly uncommon but it may be compressed by the hematoma from above.

Cerebellar hemorrhage is surgically amenable to evacuation and potentially disastrous if left untreated because the sudden increase in the intracranial pressure may lead to herniation and sudden death.

The most consistent symptom is inability to walk. Few patients may find it difficult to even sit or stand and may lean toward the side of lesion. Vomiting is frequent owing to the structural distortion of the vomiting centre. Occipital headache is also common. Dysarthria, hiccups, and tinnitus occur, but are less common .Loss of consciousness occur little late along the course but if it occurs, it carries poor prognosis.

Other Neurologic signs include (1) an ipsilateral abducens or gaze palsy toward the side of the hematoma; (2) small pupils, with the ipsilateral pupil slightly smaller; (3) rebound overshoot of the rapidly elevated ipsilateral arm; and (4) gait ataxia. Hemiparesis rarely occurs in patients with cerebellar hemorrhage, but cerebellar lesions do produce an apparent asthenia or slowness of the affected limbs. The deep tendon reflexes are symmetrically exaggerated with a normal plantar response. Typical pendular knee jerk occurs. The other signs of cerebellar incoardinaton are rare.

The signs of brain stem compression are often present in large cerebellar hematomas. Even though coma is not present on admission these patients relatively have poor prognosis without surgical intervention. In a retrospective analysis of patients with acute cerebellar hemorrhage Brennan et al found out that in patients with signs of brain stem compression 80% rapidly developed coma .About 25% of these patients slipped into coma within 3 hours of admission.(102). Only 20% had uneventful recovery.

In the series of Fisher et al only 2 of 18 patients had a benign course. The other 16 patients developed coma, usually within a few hours.

Medullary compression causes vasomotor disturbance and respiratory arrest. If they are not intervened promptly they invariably die of brain stem compression.In contrast to bleeding into cerebellar lobes, vermian hemorrhages are a rare entity. It causes usually sudden death.

The outlook of smaller cerebellar hemorrhage is excellent and recover with very little residual deficit. Even in larger hematomas, if surgical intervention is undertaken before the event of reduced consciousness, the recovery is usually good (103).

DIAGNOSIS, PROGNOSIS, AND TREATMENT

Diagnosis

The bedside diagnosis of ICH is usually made without difficulty in patients with symptoms such as headache and vomiting alongside slowly progressing, non fluctuating neurological deficit. Underlying predisposing factors such as hypertension, bleeding diathesis, drug abuse etc. helps in increasing diagnostic accuracy.

Non enhanced Computed tomography of brain is invaluable in the diagnosis of ICH. Acute blood provides dense contrast in the CT. Serial CT

scans can be used to assess the progressing neurological deficit to rule out expanding hematoma. (104).

In CT-angiography, the presence of central enhancement within the acute ICH, called spot sign has been purported as an predictor of hematoma expansion (105).

The age of the bleed can be assessed on the basis of characteristic features on the CT or MRI pictures. Initially hematomas show smooth borders. In the first 48 hours the hematoma are partially liquid thereby demonstrating a fluid level. The edema surrounding the hematoma produces an area of hypodensity around the hematoma for the first 3 days or longer. During the first few days there is considerable mass effect produced by the hematoma and edema. As the blood gets absorbed, the hematoma acquires an irregular outline which can be enhanced by contrast administration. This process starts in the periphery. There is reduction in the edema during this period. The blood in the ventricles disappears by 5 weeks. By 9 weeks, only a local circumscribed slight hypodensity remains.

The CT is sensitive for acute hemorrhage but MRI is much more sensitive for chronic lesions.Acute hematomas are isointense or hypointense on T1-weighted scans, sometimes with a darker hypointense rim, and they are bright and hyperintense on T2-weighted images. Later, the center of the hematoma appears dark on T2 and is surrounded by a bright rim. Chronic hematomas are bright on T2-weighted images (106).

Angiography is generally unnecessary unless the lesion is in an unusual locus or the patient has no risk factors for hemorrhage, such as hypertension or bleeding diathesis. Catheter subtraction angiography is used to show AVMs or aneurysms that might have caused ICH. Angiography can also suggest the likelihood of hematoma enlargement. Extravasation of contrast during angiography correlates well with subsequent enlargement of the hematoma and poorer outcome (107). MR and CT angiography can be used in a similar fashion.

Prognosis

The three most important predictors of outcome after ICH are size of hemorrhage, site of bleeding and state of consciousness of the patient at presentation. Hemorrhage expansion also indicates a worse prognosis when the hematoma attains a large size. Size and locale of the lesion on brain imaging scans renders very useful prognostic information. In putaminal hemorrhages, lesions larger than 140 mm2 in one slice have a poorer outcome. In thalamic hemorrhage, lesions larger than 3.3 cm in maximal diameter have a poor prognosis, as do cerebellar lesions larger than 3 cm.

In six additional studies, large-volume hematomas were associated with a poor outcome. Pulse pressure, admission blood pressure, and level of consciousness, as measured by the Glasgow Coma Scale, are also important prognostic variables (108).

High systolic, mean blood pressure, and pulse pressure correlate with poor outcome. The presence of hydrocephalus in patients with supratentorial hemorrhages is also an adverse prognostic sign (109).

In the chronic phase, if the patient with ICH has survived, the prognosis for recovery is actually much better than brain infarcts of similar size and location. Hematomas have dissected and separated the cerebral cortex and other brain parts, but usually the surrounding cortex is preserved. In contrast, infarcts leave dead, nonfunctioning cortex when they heal. Unlike SAH, recurrence of ICH during the acute illness is rare. These simple facts dictate the approach to ICH treatment-that is, aggressively try to limit the expanding hematoma to prevent death and late morbidity.

Treatment

The medical treatment is aimed at reducing the chance of hematoma expansion and reducing the cerebral edema and intracranial tension. Increased ICP causes decreased responsiveness and hypoventilation; in turn, hypoventilation causes a low arterial oxygen tension and high carbon dioxide tension, which lead to vasodilatation and further increase in ICP. Maintenance of a good airway and mechanical hyperventilation can reverse the process and quickly lower ICP.

Control of systemic blood pressure helps stop intracranial bleeding, but must be done cautiously. In some patients with ICH, systemic blood pressure is further increased to ensure adequate perfusion of the brain. Increased ICP

causes increased venous pressure, so elevated arterial pressure is needed to overcome the increased venous pressure to perfuse the tissues. Overzealous lowering of blood pressure can lead to under perfusion and clinical deterioration. Blood pressure should be lowered quickly, but not to hypotensive levels. Patients must be watched carefully during the treatment. Guidelines from the Stroke Council of the American Heart Association recommend maintaining the mean arterial pressure below 130 mm Hg (110). The perihematomal edema volume peaks during the third or fourth day after bleeding. The release of iron-containing breakdown products of hemoglobin likely contribute to the development of edema. Elevation of the head of the bed, hyperventilation, temperature control, and ventricular drainage have also been used to control increased ICP (111).Few data exist, however, about the effectiveness of these strategies. Concern exists that hypertonic agents could diffuse into the ICH and cause a secondary increase in volume of the hematoma because of ingress of fluid.

Langfitt noted that mannitol and forced hyperventilation were effective in reducing ICP in a group of patients with ICH. Poungvarin et al studied the usefulness of dexamethasone treatment in patients with supratentorial ICH in a double-blind randomized trial. They found that it did not improve mortality; and infections and diabetic complications were more often found in the corticosteroid-treated group (112).

When considering surgery and other therapies, hematomas, in practice, can be divided into the following three main groups:

1. Massive, rapidly developing lesions that effectively kill or devastate patients before they reach the hospital. For these lesions, little can or should be done.

2. Small hematomas, from which the patient will make an excellent spontaneous recovery. Treatment consists of controlling the etiologic factors, such as hypertension, to prevent recurrences.

3. Medium-sized hemorrhages (hematoma volumes between the two extremes) with developing mass effect after the patient reaches the hospital. Within this third group, medical measures and surgery are most helpful. Because hematomas represent the development of so-called benign masses, the logical treatment for life-threatening lesions is surgical drainage. The factors outlined in the following should be considered in deciding on surgical therapy.

Size

Hematomas larger than 3 cm in their widest diameter have a higher mortality and a more delayed recovery rate than smaller lesions. Thus, the larger the lesion on CT, the more logical its drainage would be.

Location

Some hematomas are more accessible surgically, such as those in the cerebellum and cerebral lobes. Although putaminal hemorrhages can be drained through the sylvian fissures and insular cortex, large left basal-ganglionic hemorrhages usually leave patients aphasic and dependent. Thus, treatment

should be less aggressive than for right-sided lesions. Cerebellar ICH can cause respiratory arrest without preceding gradual deterioration of neurologic function or alertness, and surgical removal of a portion of the cerebellum often leaves no important residual handicap. For these reasons, the threshold for recommending surgery for cerebellar hematomas is lower than other lesions of comparable size. Cerebellar, lobar and right putaminal hemorrhages are most accessible to surgical drainage.

Mass Effect and Drainage Pattern

Presence of mass effect necessitates surgical drainage. In older patients, despite large volume of hematoma, mass effect may be very little because of coexisting brain atrophy. The cranial cavity can accommodate excess blood in these individuals without much increase in intracranial tension. In some cases of ICH, the blood may spontaneously decompress itself into the ventricle. The degree of edema also varies with the lesions. Hence the following factors also to be taken into consideration while deciding about the surgical drainage. They are: 1.presence of hydrocephalus, 2.compression of lateral or third ventricle by the hematoma, 3. Presence of midline shift, 4.uncal herniation, 5.effacement of ambient cisterns, and 5. Displacement of the fourth ventricle in the presence of posterior fossa ICH. Surgical drainage would be indicated more strongly for lesions with greater mass effect and no spontaneous decompression.

Etiology

The ICH caused by CAA bleeds after the surgical drainage of the hematoma because of the weak vessel wall. The surgery for ICH due to CAA is controversial. Izumihara et.al, in his study of 37 patients with CAA related ICH, found out that there is no increased mortality after surgery (113) . However they concluded that surgery does not improve the prognosis of the patients significantly .

If the underlying etiology for ICH is anticoagulant therapy, there will be continuous bleeding both per operatively and post operatively. Hence the underlying bleeding diathesis should be corrected before undertaking surgery. Although anticoagulant-related hemorrhage patients usually do worse than those with other etiologies, some patients have good outcomes after surgical drainage despite large size and midline shifts (114). In case of ICH caused by AV malformations , the underlying lesion can be removed at the same time of evacuating the hematoma . The threshold for surgical treatment should be most favorable for vascular malformations, moderatelyso for accessible lesions caused by hypertension, and least favorable for CAA or ICH caused by a bleeding diathesis.

Timing

The timing for surgical drainage is not clearly established. Theoretically the blood in the hematoma remains in liquid state and can be easily aspirated during the initial 3 days. However a study designed to test the hypothesis by Morgenstern et al was stopped owing to the increased mortality in the early

surgical arm because of the increased incidence of rebleeding. In their study, rebleeding occurred in 40 % of the patients treated by surgery within 4 hours and 12% of patients treated within 12 hours. The mortality rate was very high among the patients who rebled.(115).Thus they concluded that early surgery promotes rebleeding and thus associated with high mortality.

After 7 to 10 days, the hematoma softens and is amenable to aspiration. However, patients who survived after one week can have spontaneous improvement once the edema subsides. In these patients the advantage of late surgery offers questionable benefit. But if the patient has underlying AV malformation, surgery for removal of the lesion is advocated. Whether late surgery improves the outcome or hastens recovery is not known. Thus the guidelines for surgical management on the basis of timing are not clear.

Clinical Course

The most important determinant to be considered in selecting patients for surgery is the clinical detoriation of the patient. The emergence of brain stem compression signs carries poor prognosis and should be strongly considered for emergency surgery if the lesion is surgically accessible.

In evaluating the efficacy of surgical vs. medical decompression in STICH trial, investigators found out non superiority of early surgery against conservative medical management (116). In this single centre randomized control study, Morgenstern et al randomized 1033 patients into two groups one receiving early surgery and other for conservative treatment. Among the early

surgery group who underwent surgery within 24 hours, 28% had favorable outcome than in the other conservative treatment group which had 24% in terms of favorable outcome.

Various Meta analysis and other investigators also found no significant benefit for early surgery compared to conservative treatment.

In various series, depressed level of consciousness is the single most important predictor of outcome as measured by Glasgow coma scale. Large hematoma volume (60 mL), midline shift, effacement of the contralateral perimesencephalic and ambient cisterns, and dilatation of the contralateral temporal horn of the lateral ventricle were the other predictive features. Patients who deteriorate during the first 12 hours usually have enlargement of hematoma on follow-up CT scans. Those that deteriorate after the first day usually do so because of brain edema around the hematoma.

Treatment strategies to reduce iron related neurotoxicity:

DEFEROXAMINE.

Deferoxamine is isolated from streptomyces pilosus as an iron chelate and chemically treated to remove the metal ligand. It had high affinity for the ferric iron with low affinity for calcium. It removes iron from hemosiderin and ferritin and to a lesser extent from transferrrin. Iron in the hemoglobin or cytochromes are not removed. Deferoxamine mesylate (deferral mesylate) is poorly absorbed orally and mostly administered parenterally.

Dosage;

IV dose is 10 -15 mg /kg/hr by continuous infusion.

IM dose is 50 mg /kg with the maximum of 1 g.

Rapid IV boluses are associated with hypotension. It can also occur with IM route. Deferoxamine is metabolized by plasma enzymes and readily excreted in urine.

Deferoxamine causes a number of allergic reactions, including pruritis, rash, and anaphylaxis. Other adverse effects include dysuria, diarrhea, fever, leg cramps, and tachycardia. Occasional cases of cataract formation have been reported. Deferoxamine may cause neurotoxicity in the longrun, both visual and auditory changes have been reported (117).

Deferiprome is an orally acting iron chelator. Deferasirox is a tridentate chelator with a high affinity for iron and low affinity for other metals. It is orally active and well absorbed. It binds iron in the circulation and the compound is excreted in bile.

DFX and rat ICH.

Masanobu et al in 2009 found out, administration of >10mg/kg of deferoxamine to experimentally induced ICH in rats reduced brain edema, neurlogical deficits and death.In another study published on 2010, Masanobu and coworkers found out beneficial effect of DFX 50mg/kg in 344 rats following experimentally induced ICH. They found out the therapeutic window

of DFX for acute perihematomal brain edema formation is 12 hours. The DFX treatment window for long term brain atrophy is 24 hours. The optimal therapeutic window is 7 days (118).

DFX in pigs

In an another study using 16 male piglets,Yuxiang gu MD and coworkers found deferoxamine at the dose of 50mmg/kg IM reduced the intracerebral hematoma induced iron accumulation and neuronal death in treated piglets (119).

DFX and humans.

The safety and tolerability of DFX has been studied in humans. Magdy selim and coworkers conducted a phase 1 multicentre dose finding study in twenty patients admitted with ICH.The patients were enrolled onto 5 dose tires starting with 7 mg/kg/day and ending with 62mg/kg/day as the maximum tolerated dose. In that study DFX was discontinued in 2 subjects (10%) because of adverse events.6 subjects (30%) experienced serious adverse events none of them are related to the drug. Based on that study, they concluded that daily infusions of DFX after ICH are feasible, well tolerated and are not associated with serious events and mortality. Fifteen percent of the patients had modified

Rankin score of <2 and 39% had modified Rankin score of 4 to 6 .On day 9, 0.15% of them died(120) .

ERYTHROPOIETIN.

In a preliminary study, involving healthy volunteers, Damian and coworkers of Denmark studied the ferritin lowering effect of EPO. They administered 5000IU of EPO and 100 mg/day of ferrous sulphate to healthy volunteers. They found hematocrit increased substantially by 12 weeks. By week 6, plasma concentrations of ferritin, total iron and transferrin saturation reached a nadir.EPOs ability to deplete iron stores and reducing its availability to catalyze the free radical formation may offer neuroprotection to the at risk neurons. It may be the reason for EPOs potent antioxidant, antiexcitotoxic, antiapoptotic and neurogenic properties (121).

TIRILAZAD MESYLATE:

It is a synthetic, lipid soluble 21 – amino steroid molecule devoid of any glucocorticoid activity, that has been tested as a neuroprotectant in acute stroke, SAH and traumatic brain injury. It belongs to the class of Lazaroids. The main mechanism of action is by inhibition of iron dependent lipid peroxidation by the following mechanism,

1.free radical scavenging.

2.reducing the formation of hydroxyl radical.

3.decreasing membrane phospholipid fluidity.

4.maintaining endogenous antioxidant levels ,especially Vitamin E and C.

In a systemic review published by TRILIZAD INTERNATIONAL STEERING COMMITTEE REVIEW by Prof.Bath et.al, it has been concluded that Trilizad mesylate increased mortality and morbidity in about one fifth of the patient. This conclusion is based on the review of the 4 clinical trials (122). Other drugs that has putative neuroprotection , but associated with poor outcome in clinical trials include,

1.Selfotel – a glutamate receptor antagonist,
2.Enlimomab- an anti intercellular adhesion molecule antiboby,
3.Diaspirin linked hemoglobin,
4.Aptigenel –NMDA receptor blocker,
5..calcium channel blockers such as nimodipine, flunarazine etc,
6.Eliprodil- NMDA receptor antagonist,
7.Lubeluzole – a molecule with nitric oxide modulating activity,
8.GV 150526 –glycine receptor antagonist.

Calculating the volume of ICH :

The volume of the hematoma can be accurately measured by on the bedside in a plain CT brain by using the formula of ellipsoid. In the parenchyma , the hematoma assumes the shape of a ellipsoid. The simplified formula of the ellipsoid is ABC/2.

VOLUME OF ICH IN ml = A X B X C /2,

Whereas,

A = the largest cross-sectional diameter .

B= the largest diameter perpendicular to A on the same slice .

C = the approximate number of 10 mm slices on which the ICH is seen

/2 = added to approximate the volume of an ellipsoid .

The slice of the CT in which the hematoma is seen largest should be selected as an index slice. A & B are measured in centimeters to the nearest 0.5 cm. in other slices if the diameter is more than 75 % of the index slice, it is counted as one slice. If the diameter is between 25 to 75 %, the silce count is 0.5. the slices with diameter less than 25 % should be ignored. Similarly , if thickness of the slice is 0.5 mm , the total number slices should be divided by 2. Kothari et .al . demonstrated that the volume of ICH can be accurately measured by this method in less than one minute (123).

Gabel et al compared the ABC/2 formula with computer volumetric analysis and concluded that they are comparable in accuracy in measuring the volume of hematoma if the borders of the hematoma are comparably rounder (124).

Hattner et .al . suggested the denominator of 3 instead of 2 in anticoagulation related hemorrhage , because most of the hemorrhage assumes multilobulated appearance (125).

Modified Rankin scale:

The Rankin scale was first introduced by Rankin in 1957 (126) to assess the disablity and dependency after a atroke. It was later modified by Lindley *et al* in 1994 (127).

The scale 0 is the state of perfect health and scale 6 is death.

0 - No symptoms.

1 - No significant disability. Able to carry out all usual activities, despite some symptoms.

2 - Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.

3 - Moderate disability. Requires some help, but able to walk unassisted.

4 - Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.

5 - Severe disability. Requires constant nursing care and attention, bedridden, incontinent.

6 - Dead.

MATERIALS AND METHODS

Venue

This study was conducted in the Institute of Internal Medicine at Rajiv Gandhi Government General Hospital , Madras Medical College, Chennai from May 2012 to November 2012.

Study Design

This was a hospital based observational study.

Sample Profile

A group of 50 subjects participated in this study.

Inclusion criteria for study patients

First episode of Primary supratentorial hemorrhage diagnosed clinically and by computed tomography of brain.

Exclusion criteria for study patients .

1. Ischemic stroke,
2. Anemia ,
3. Severe alcohol consumption,
4. Chronic liver disease.
5. Chronic kidney disease.
6. Hematological cancer.
7. Secondary intracerebral hemorrhage.

STUDY PROTOCOL

1. Clinical Evaluation

A standard proforma designed for the study was used. On admission, a complete history was obtained from every patient including symptoms of headache, vomiting, loss of consciousness, seizures and focal neurological deficit. History of hypertension , diabetes mellitus , drug history including use of anticoagulation were noted. Clinical evaluation was carried out noting vital parameters, clinical signs of focal neurological deficit and signs of increased intracranial tension. Glasgow coma scale was used to assess the stroke severity. Other systems were also examined to find significant comorbidities. All patients were treated according to the established guidelines at the time of study.

2.Radialogical evaluation:

All the patients were subjected to non enhanced computed tomography scan of the brain. Primary intracerebral hemorrhage located in the supratentorial region were selected. The location of the hematoma, presence of midline shift and intraventricular extension of bleed were assessed. The size of the hematoma was calculated using the Ellipsoid Formula.

3. Assay of Biochemical Parameters

After getting informed consent from all the participants, 2ml of venous blood was collected by sterile venepuncture within 72 hours of symptom onset. Serum ferritin levels were estimated by ELISA method. Simultaneously

renal function , liver function and complete blood count and peripheral smear study were carried out.

4. Evaluation of prognosis

All the study patients were assessed using the modified Rankin scale at the end of first week and at the end of one month follow up. The score of 0-2 was considered good prognosis. The score of 3-5 was considered bad prognosis and the score 6 was given to the event of death.

5.Statistical Analysis:

The variables were analysed using SPSS software version 15. Students 't' test and chi square tests were employed to find out significance of difference between means in study patients. Variables are analysed using one way ANOVA between different prognostic groups.Spearman's correlation analysis was used to find correlation between serum ferritin and GCS and volume of hematoma.

7.Estimation of serum ferritin levels using quantitative ELISA ferritin test system:

Principle

This is the classic sandwich ELISA assay using *ACCUBIND SERUM FERRITIN KIT OF MONOBIND INC.U.S.A.* It is IMMUNOENZYMOMETRIC SEQUENTIAL ASSAY TYPE 4.

The essential reagents required for an immunoenzymometric assay include high affinity and specificity antibodies (enzyme and immobilized), with different and distinct epitope recognition, in excess , and native antigen. In this procedure , the immobilization takes place during assay at the surface of a microplate well through the interaction of streptavidin coated on the well and exogenously added biotinylated monoclonal anti- ferritin antibody.

Upon mixing monoclonal biotinylated antibody, and a serum containing the native antigen, reaction results between the native antigen and the antibody, forming an antibody – antigen complex. Simultaneously the biotin attached to the antibody binds to the streptavidin coated on the microwell resulting in immobilization of the complex. The reaction is illustrated by the following equation;

$$Ag(ferritin) + {}^{btn}Ab(m) \leftrightarrow Ag(ferritin) - {}^{btn}Ab\ (m). \text{----1}$$

$^{btn}Ab(m)$ = biotinylated monoclonal antibody (excess quantity).

Ag(ferritin) = native antigen (variable quantity).

$Ag(ferritin) - {}^{btn}Ab\ (m).$ = antigen antibody complex.
(variable quantity).

$$Ag(ferritin) - {}^{btn}Ab\ (m).+ streptovidin_{cw} ===> \text{immobilized complex (ic)----2}$$

$streptovidin_{cw}$ = streptovidin immobilized on well.

Immobilized complex (ic) =Ag-Ab bound to the well.

After a suitable incubation period , the antibody-antigen bound fraction is separated from unbound antigen by decantation or aspiration. Another antibody (directed against different epitope) labeled with an enzyme is added . Another interaction occurs to form an enzyme labeled antibody-antigen-biotinylated-antiody complex on the surface of the wells. Excess enzyme is washed off via a wash step. A suitable substrate is added to produce color, measurable with the use of a microplate spectrophotometer. The enzyme activity on the well is directly proportional to the native antigen concentration. By utilizing several different serum references of known antigen concentration , a dose response curve can be generated from which the antigen concentration of an unknown can be ascertained.

$$(IC) + {}^{enz}Ab(ferritin) \leftrightarrow {}^{enz}Ab(ferritin)\text{-}IC \quad \text{-----3.}$$

^{enz}Ab(ferritin) = enzyme labeled antibody (excess quantity).

^{enz} Ab(ferritin)-IC = antigen antibody complex.

OBSERVATION AND RESULTS

Total number of subjects;50

Age wise distribution

AGE IN YEARS	Frequency	Percentage
< 40	6	12%
41 – 50	10	20 %
51 – 60	18	36%
61-70	12	24%
> 70	4	8%

Table 1. Age distribution of study population.

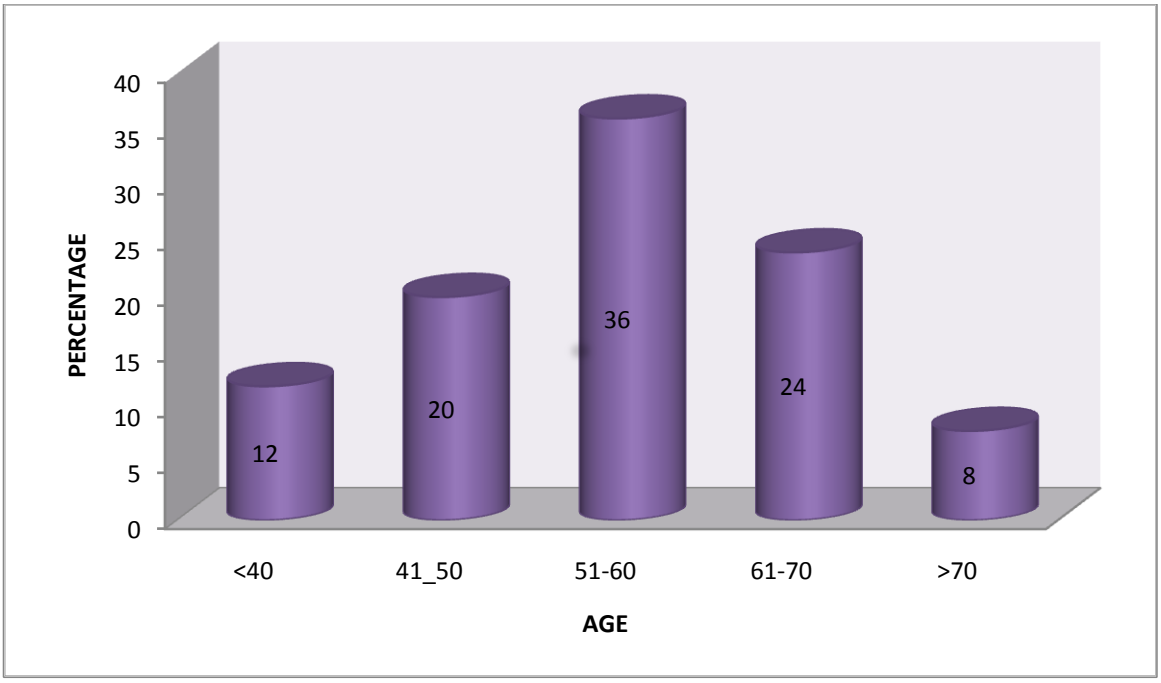

Chart 1.Age distribution of study population.

Majority of the patients belong to the age between 51 to 70 years.the minimum age was 30 years and maximum age was 80 years.

Sex distribution

Sex	Frequency	percentage
Male	39	78
female	11	22

Table 2. sex distribution of study population.

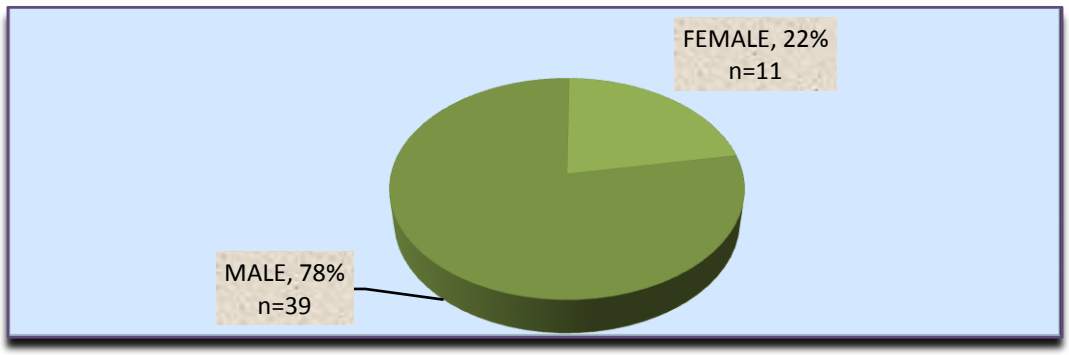

chart 2. Sex distribution of study population.

PROGNOSTIC GROUPS.

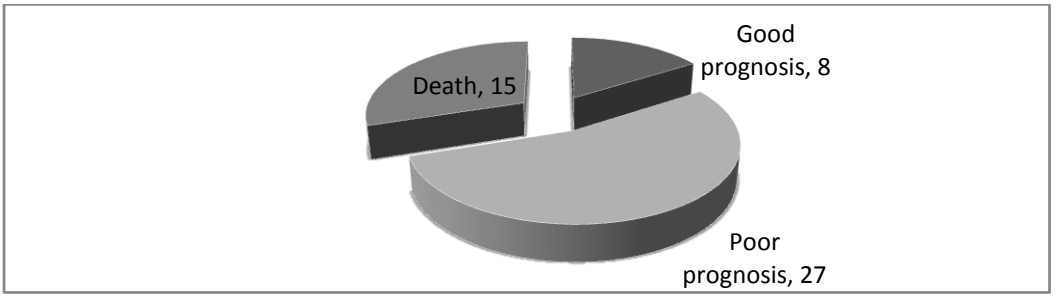

Chart 2 a. Different prognostic groups.

Total study patients = 50.

Patients with MRS < 2 (Good prognosis) = 8.

Patients with MRS 3-5 (Bad prognosis) = 27.

Patients with MRS 6 (Death) =15.

Location of hemorrhage

site	Frequency	Percentage
Lobar	11	22
Gangliocapsular	32	64
Thalamus	7	14

Table 3. location of hematoma in study population.

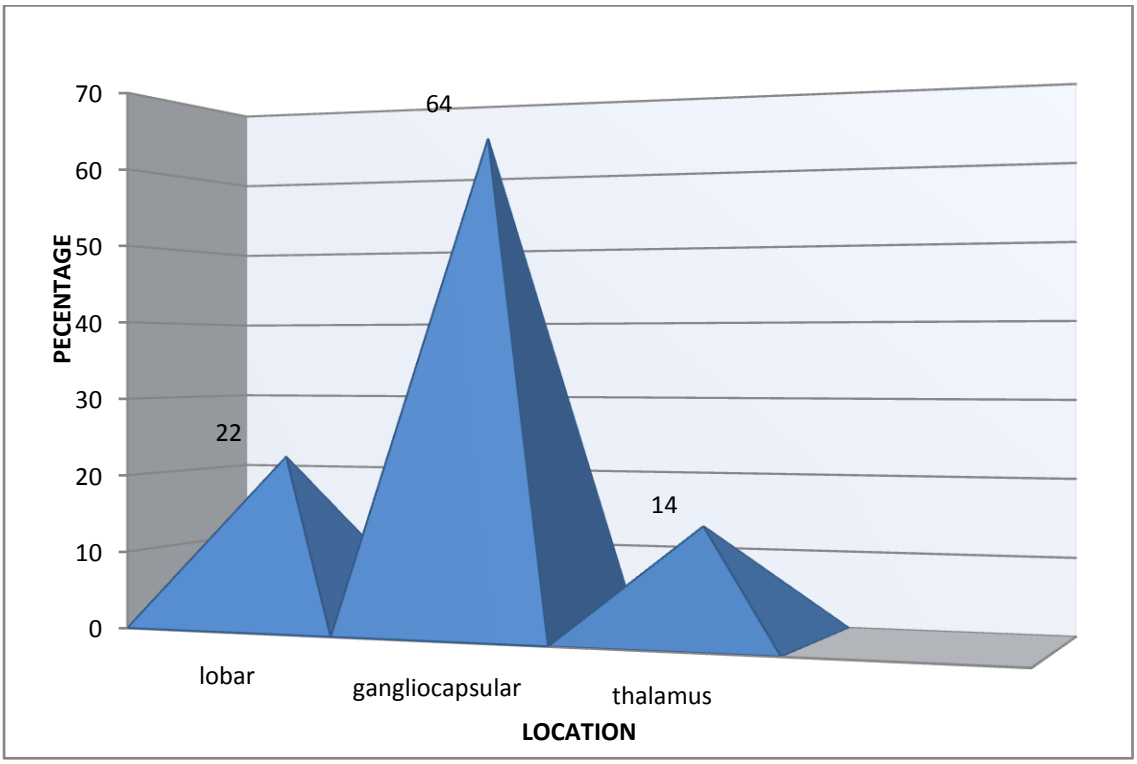

Chart 3. Location of hematoma in study population.

The most common location of hematoma in the study population is gangliocapsular region and is most consistent with the site of hypertensive hemorrhage (64 %).The thalamus is least affected in the study (14 %).

Volume of ICH

Volume (ml)	Frequency	Percentage
< 30	9	18
31 – 60	20	40
61 – 90	15	30
91 – 120	4	8
>120	2	4

Table 4. volume of hematoma.

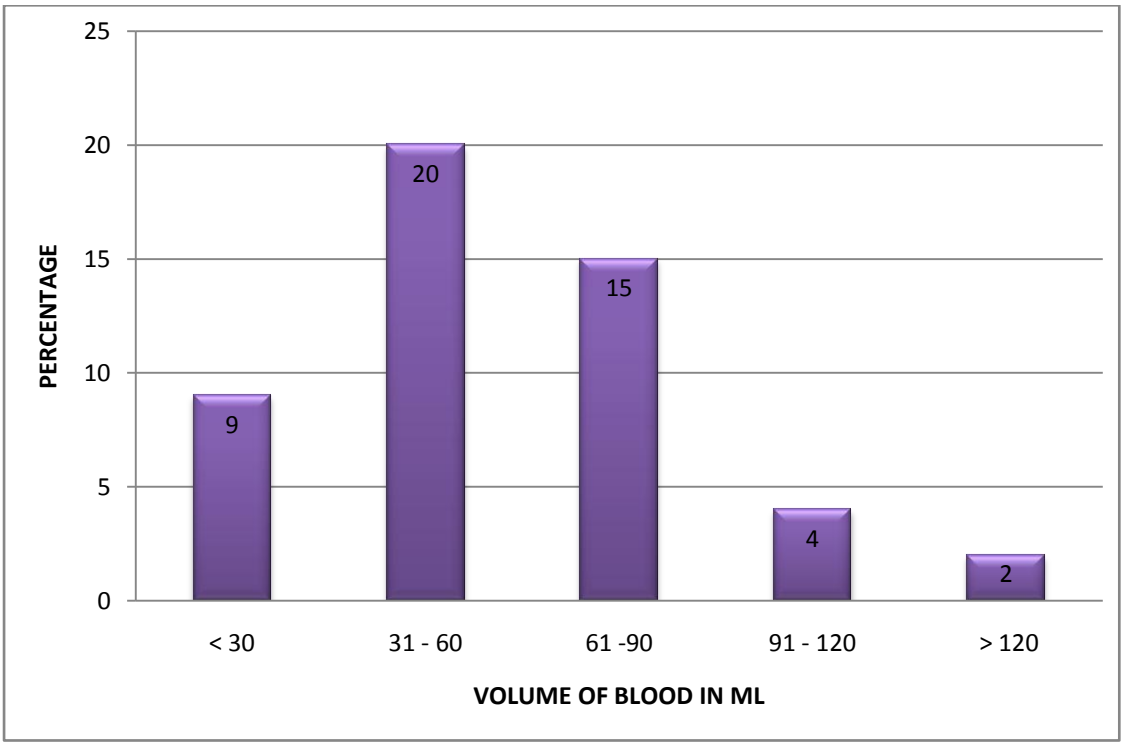

Chart 4.volume of Hematoma.

About 40 % of the study population has hematoma volume between 31 to 60 ml. The mean volume of hematoma is 59.58 ml.

Risk factors

Risk factor	Frequency	Percentage
Hypertension	49	98
Diabetes	9	18
Smoking	33	66
Alcoholism	24	48

Table 5. risk factors among the study population.

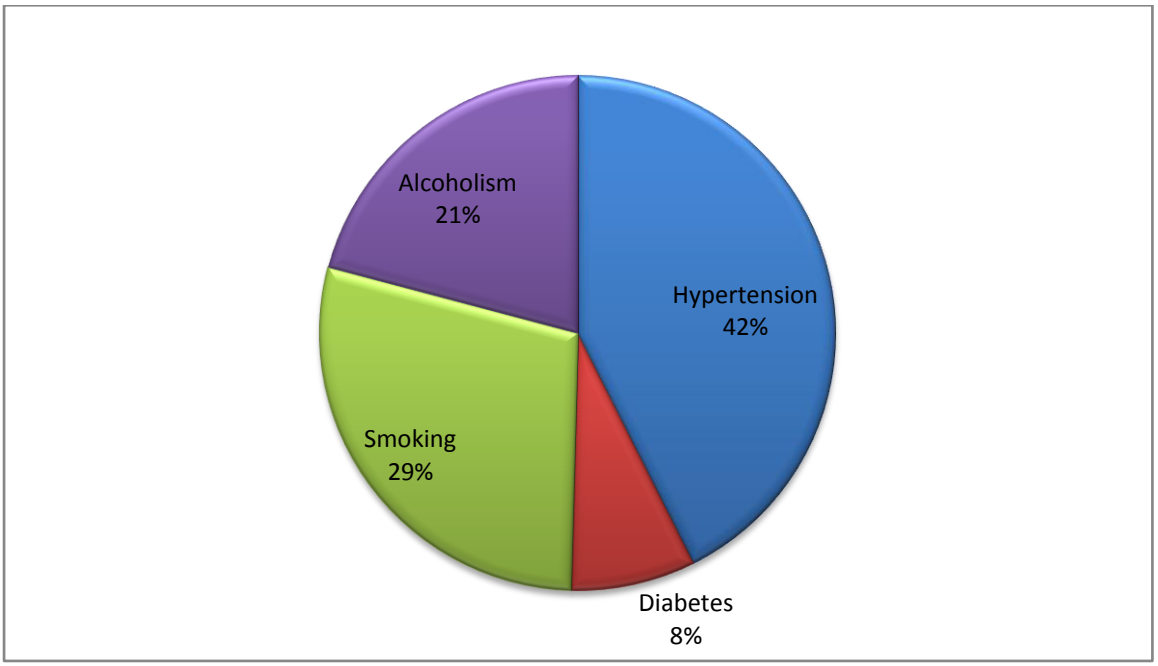

Chart 5. Risk factors among study population.

Hypertension is present in 98 % of the patients and is the most common etiology in ICH. Diabetes is present in 18 % of the study population. 43 male patients were smokers and 24 of them are alcoholic.

Symptomatology

Symptoms	Frequency	Percentage
Headache	25	50
Vomiting	15	30
LOC	10	20
Seizures	5	10
FND	50	100

Table 6. frequency of symptoms among the study population.

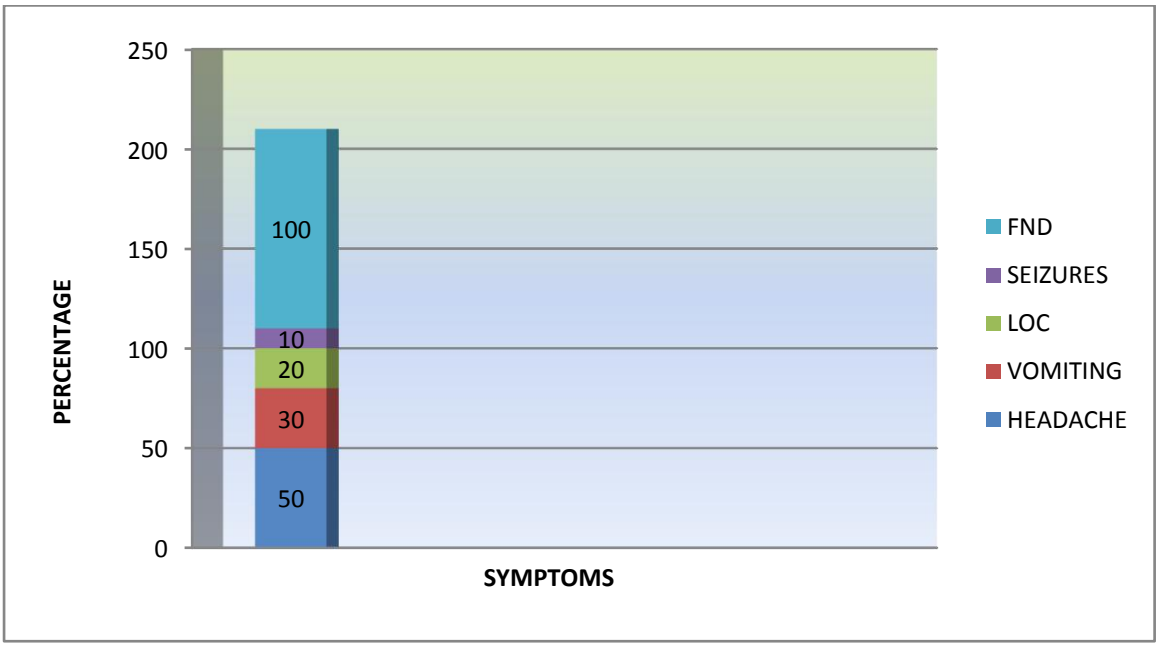

Chart 6. Frequency of symptoms among study population.

Headache is the second most common symptom after focal neurological deficit with frequency of 50%. The incidence is higher than that of quoted in other studies.

MORTALITY DATA :

Total number of subjects =50

Total number of deaths=15

Total number of survivors= 35

Age wise distribution

AGE IN YEARS	Frequency	Percentage
< 40	2	13.33
41 – 50	1	6.66
51 – 60	7	46.66
61-70	3	20.00
> 70	2	13.33

Table 7. Age distribution of mortality.

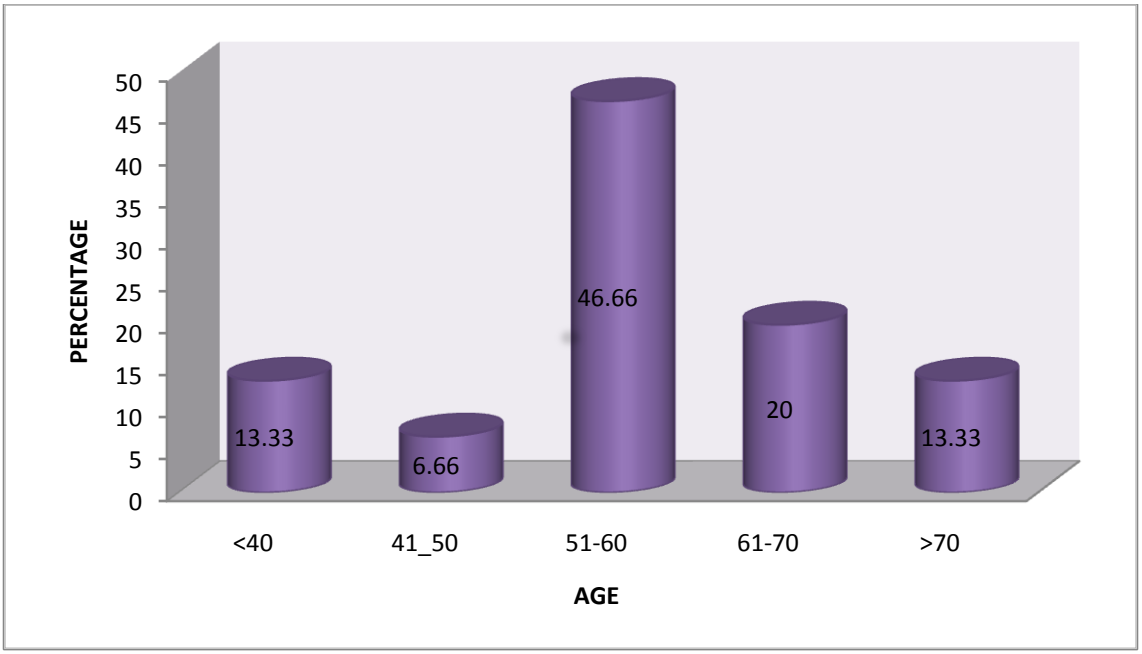

Chart 7. Age distribution of mortality. The overall mortality is 30 %.The maximum number of mortality happened among the age group of 51 -70 years accounting for 66.6%.

Sex distribution

Sex	Frequency	Percentage
Male	12	80
female	3	20

Table 8. sex distribution of mortality.

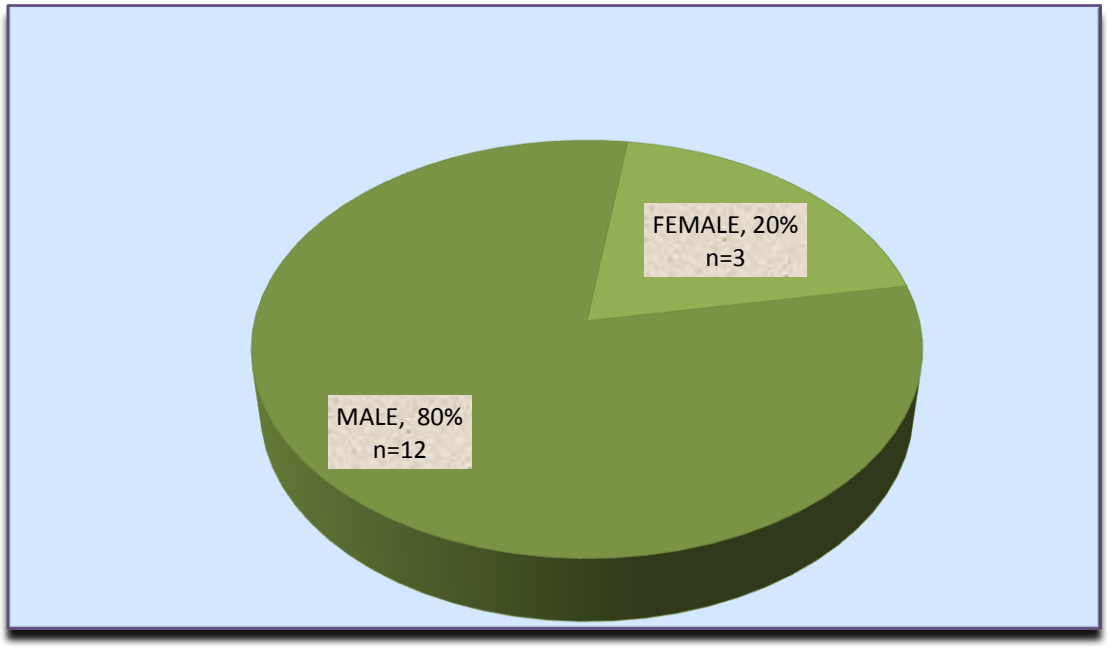

Chart 8. Sex distribution of mortality.

The mortality was high among males (34.28 %) than that of females(20 %).

Volume of ICH

Volume (ml)	Frequency	Percentage
< 30	0	0
31 – 60	4	26.66
61 – 90	8	53.33
91 – 120	2	13.33
>120	1	6.66

Table 9. volume of ICH among the dead.

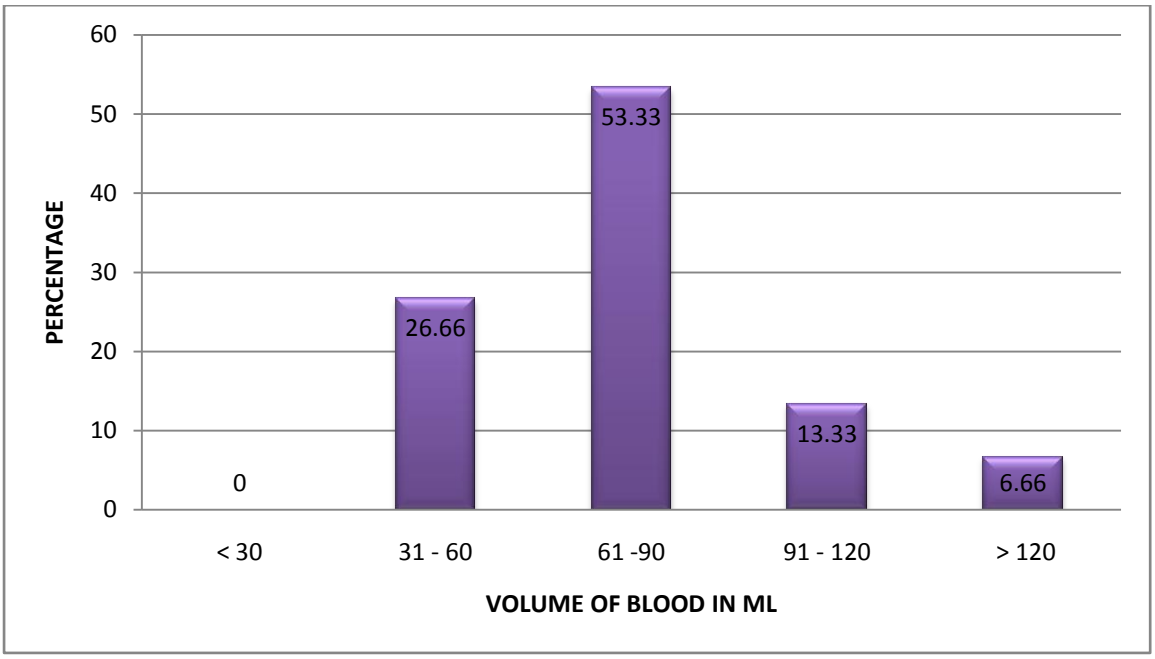

Chart 9. volume of ICH among the dead.

	frequency	Percentage
Midline shift	1	6.66
IVH	8	53.33

Table 9 a. other CT characteristics.

The mean volume of the hematoma is 78.66 ml (SD 23.295). The presence of intraventricular extension is noted in 53.33% of patients and significant midline shift in 6.6%.

Risk factors

Risk factor	Frequency	Percentage
Hypertension	15	100
Diabetes	5	33.33

Table 10. Distribution of risk factor among the dead.

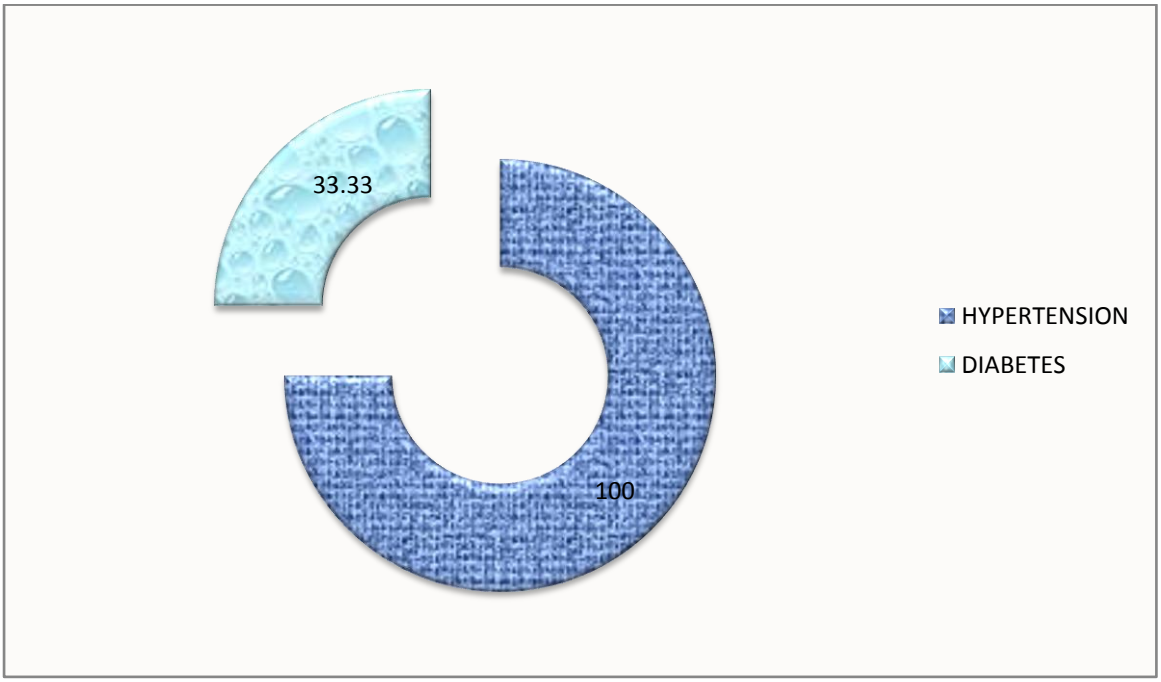

Chart 10. Distribution of risk factor among the dead.

Hypertension is present in all the patients among the dead. Diabetes is present in 33.33 5 of the patients.

Location of hemorrhage

site	Frequency	Percentage
Lobar	4	26.66
Gangliocapsular	9	60.00
Thalamus	2	13.33

Table 11. location of hematoma among dead.

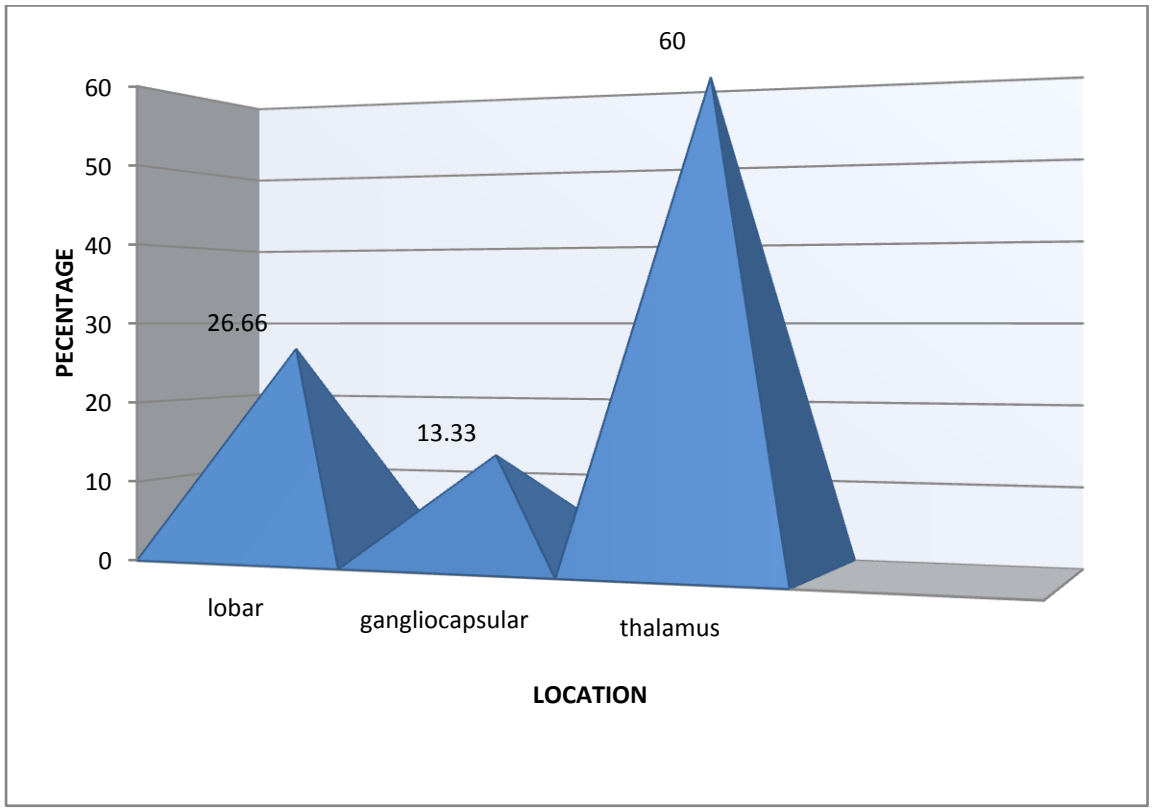

Chart 11. location of hematoma among dead.

The ganglio capsular region is the common site affected by ICH (60 %).

Serum ferritin values

Sr.ferritin (ng/ml)	Frequency	Percentage
< 200	O	O
200 – 300	2	13.33
300 – 400	9	60.00
>400	4	26.66

Table 12. serum ferritin values in the mortality group.

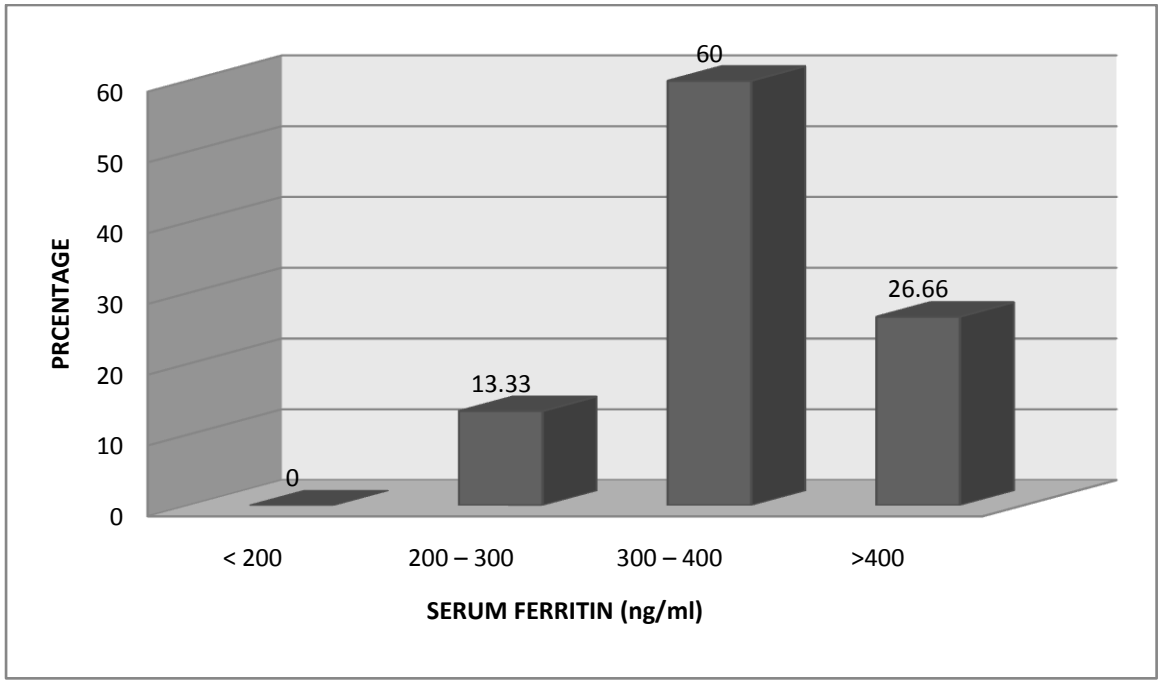

Chart 12.serum ferritin values in the mortality group.

The serum ferritin is significantly elevated in this group with MRS = 6. The mean value is 363.4 ng/ml (SD 46.14). This is statistically significant with P <0.05.

GOOD PROGNOSTIC GROUP MRS 0-2

Age wise distribution

AGE IN YEARS	Frequency	Percentage
< 40	4	50
41 – 50	1	12.50
51 – 60	2	25.00
61-70	1	12.50
> 70	0	0

Table 13. Age distribution among good prognostic group.

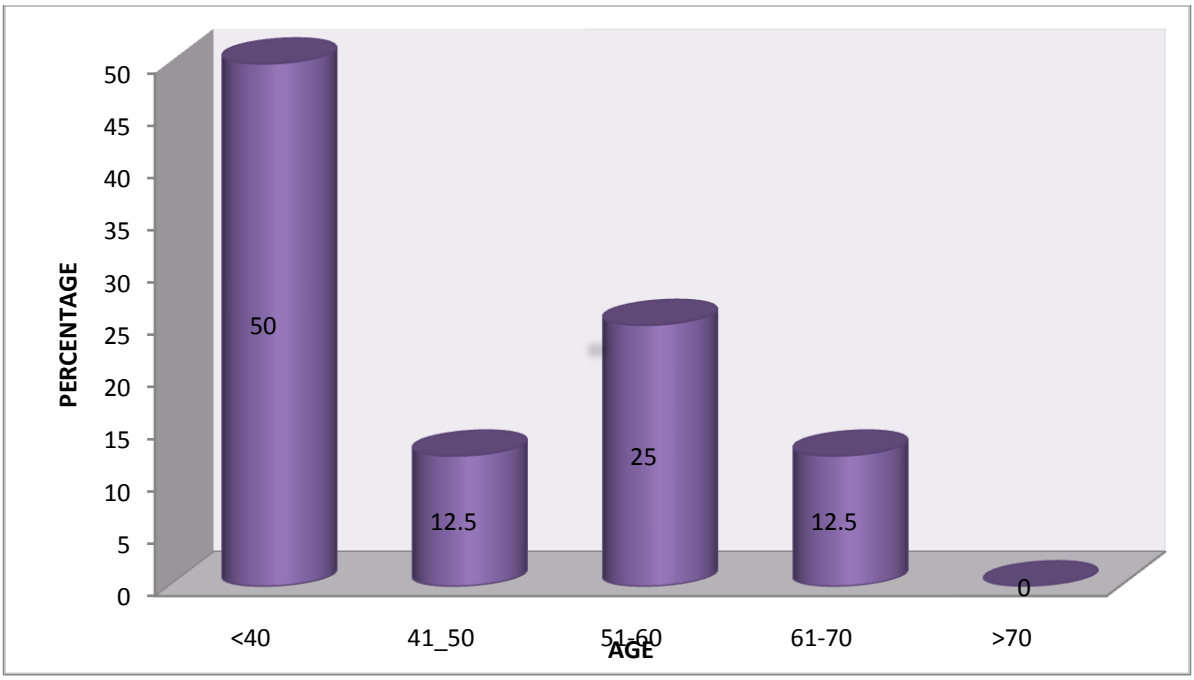

Chart 13. Age distribution among good prognostic group.

Persons less than 40 years of age has good prognosis compared to other age groups. There is no persons aged above 70 has good prognosis.

Risk factors

Risk factor	Frequency	Percentage
Hypertension	8	100
Diabetes	0	0

Table 14. risk factor among good prognosis group.

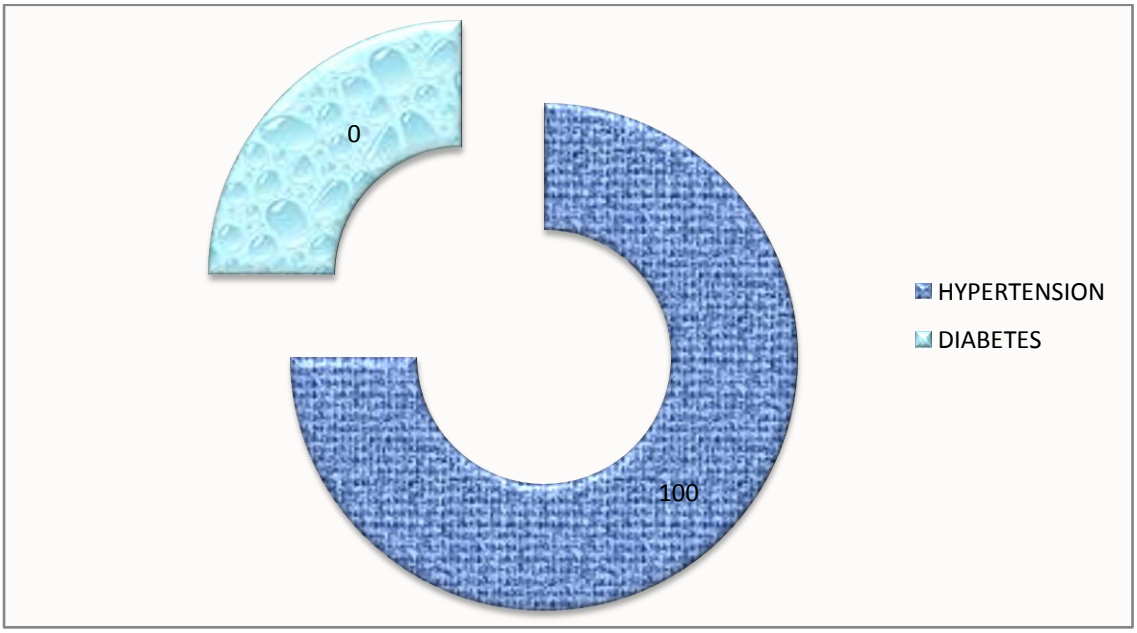

Chart 14. risk factor among good prognosis group.

The patients with no diabetes had good prognosis.

Location of hemorrhage

site	Frequency	Percentage
Lobar	0	0
Gangliocapsular	1	12.50
Thalamus	7	87.50

Table 15. Location of hematoma among good prognostic group.

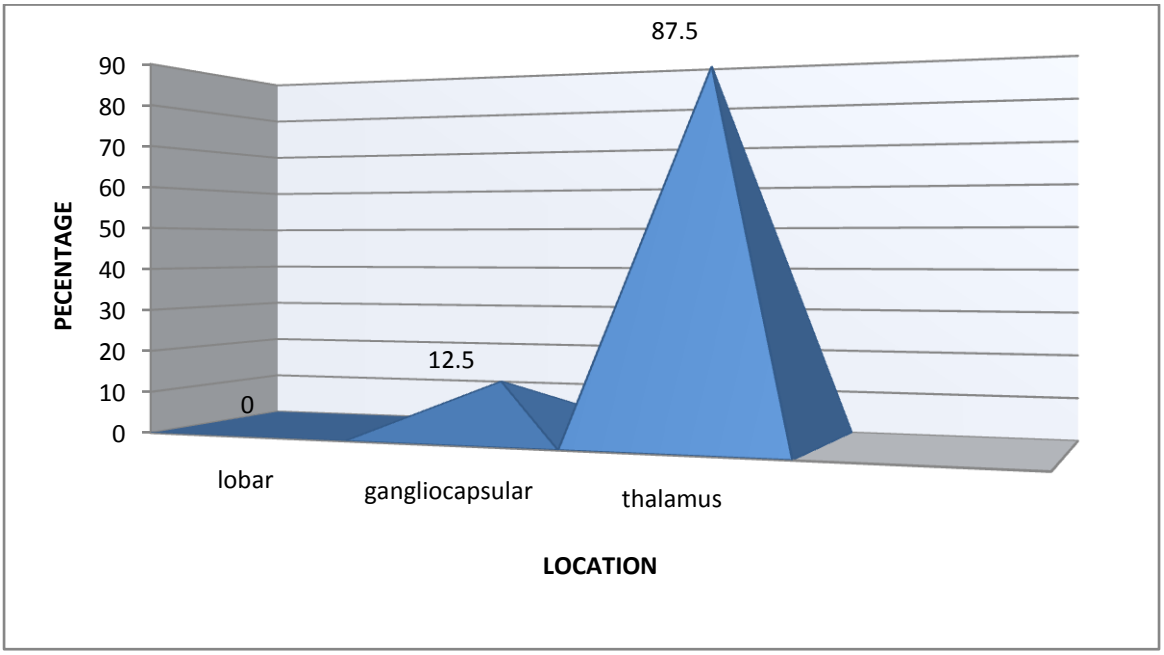

chart 15. Location of hematoma among good prognostic group.

About 87 % of the patients in the good prognostic group had their hematoma located in thalamus.

Volume of ICH

Volume (ml)	Frequency	Percentage
< 30	4	50.oo
31 – 60	2	25.00
61 – 90	2	25.00
91 – 120	0	0
>120	0	0

Table 16. volume of ICH in good prognostic group.

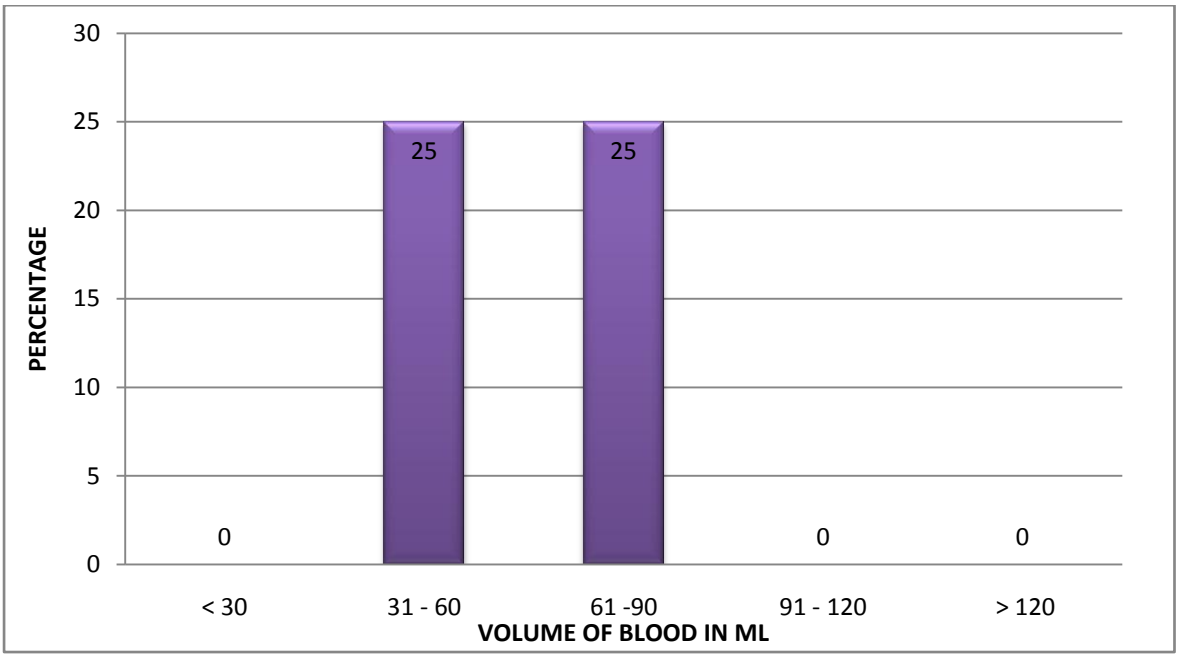

Chart 16. volume of ICH in good prognostic group.

-	Frequency	Percentage
Midline shift	0	0
IVH	0	0

Table 16 a . Other CT findings.

Most of the patient had their hematoma volume less than 30 ml (50 %). The mean volume of hematoma was 24.12 ml with SD 8.39. The difference is statistically significant ($p < 0.05$). There is no evidence of IVH and midline shift.

Serum ferritin values

Sr.ferritin (ng/ml)	Frequency	percentage
< 200	8	100
200 – 300	0	0
300 – 400	0	0
>400	0	0

Table 17. serum ferritin values in good prognostic group.

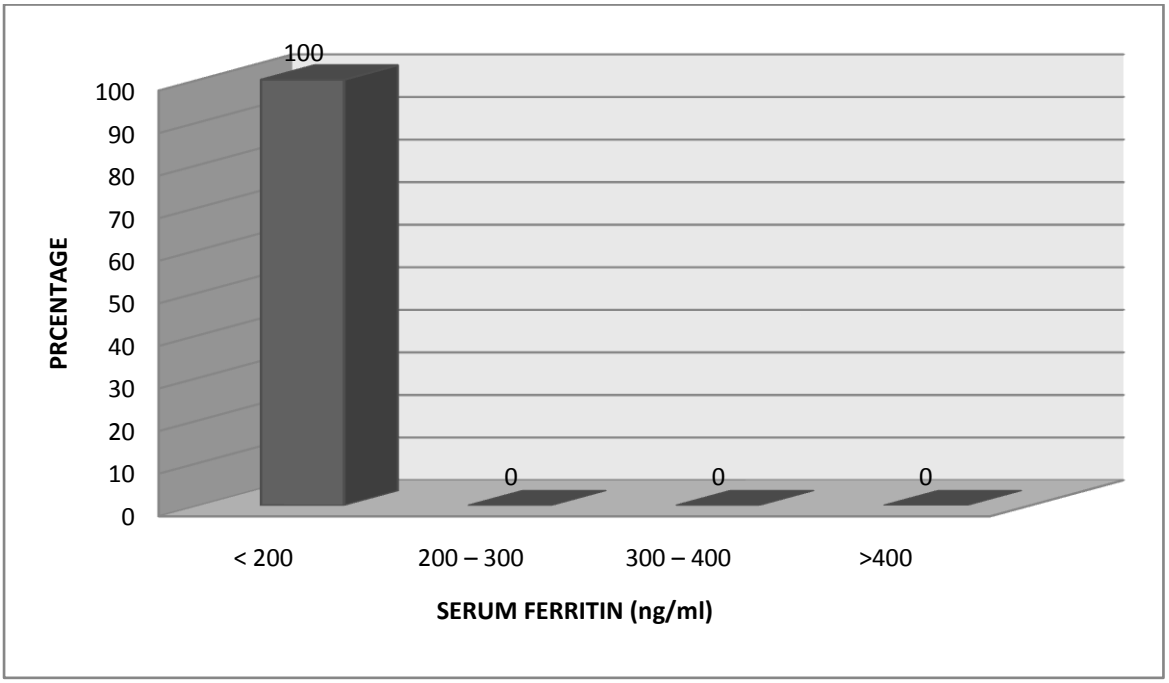

Chart 17. serum ferritin values in good prognostic group.

All 8 patients in the good prognostic group hasd their ferritin value less than 200 ng/ ml .The mean serum ferritin value was 111.0 ng/ml (SD 32.08). This is statistically significant with $P < 0.05$.

BAD PROGNOSTIC GROUP MRS 3-5 :

Age wise distribution

AGE IN YEARS	Frequency	Percentage
< 40	1	3.70
41 – 50	7	25.92
51 – 60	9	33.33
61-70	8	29.62
> 70	2	7.40

Table 18. Age distribution of patients in poor prognostic group.

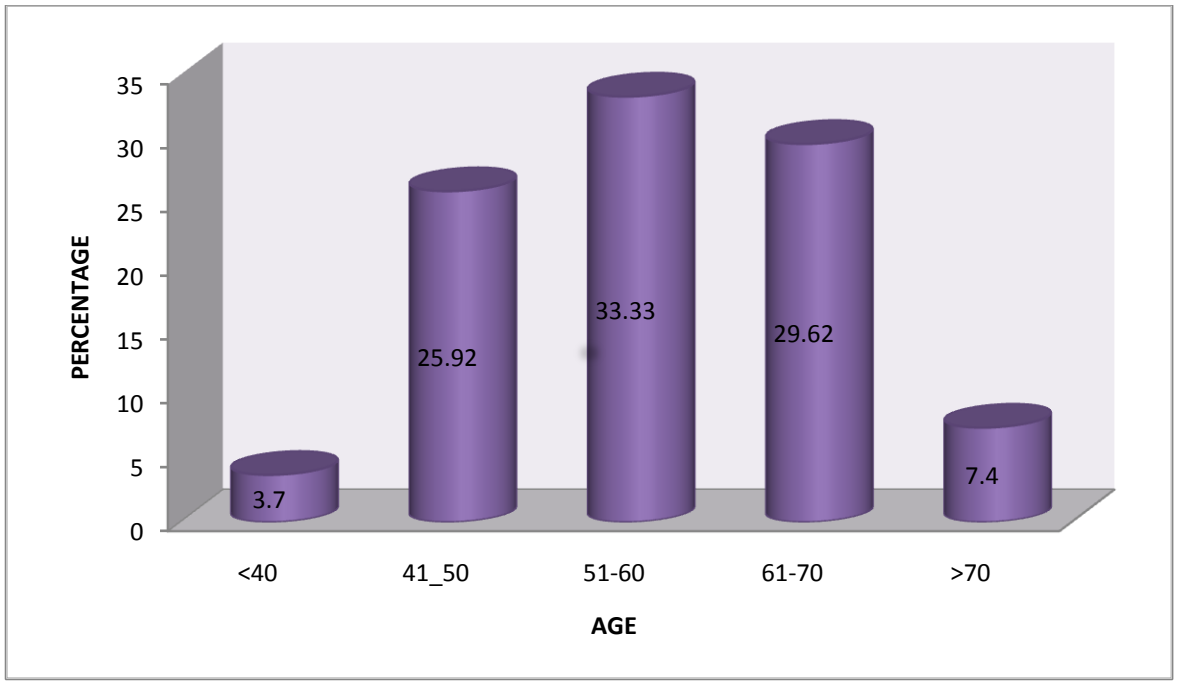

Chart. 18. Age distribution of patients in poor prognostic group.

Most of the patients with poor prognosis were within the age group of 51 to 70 years (62.95 %).

Risk factors

Risk factor	Frequency	Percentage
Hypertension	27	100
Diabetes	5	18.51

Table 19. Risk factors among poor prognostic group.

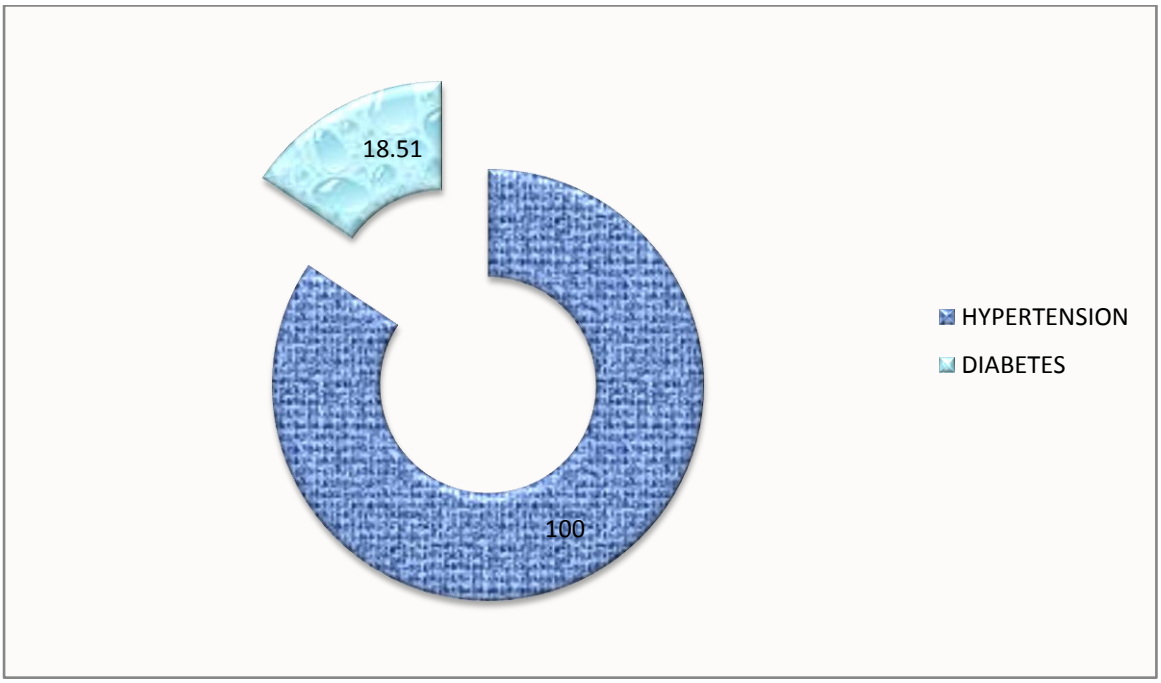

Chart. 19. Risk factors among poor prognostic group.

All patients in this group had hypertension and among 9 diabetic patients ,5 had poor prognosis (55.55 %).

Location of hemorrhage

site	Frequency	Percentage
Lobar	4	14.81
Gangliocapsular	19	70.37
Thalamus	4	14.81

Table 20. location of hematoma among poor prognostic group.

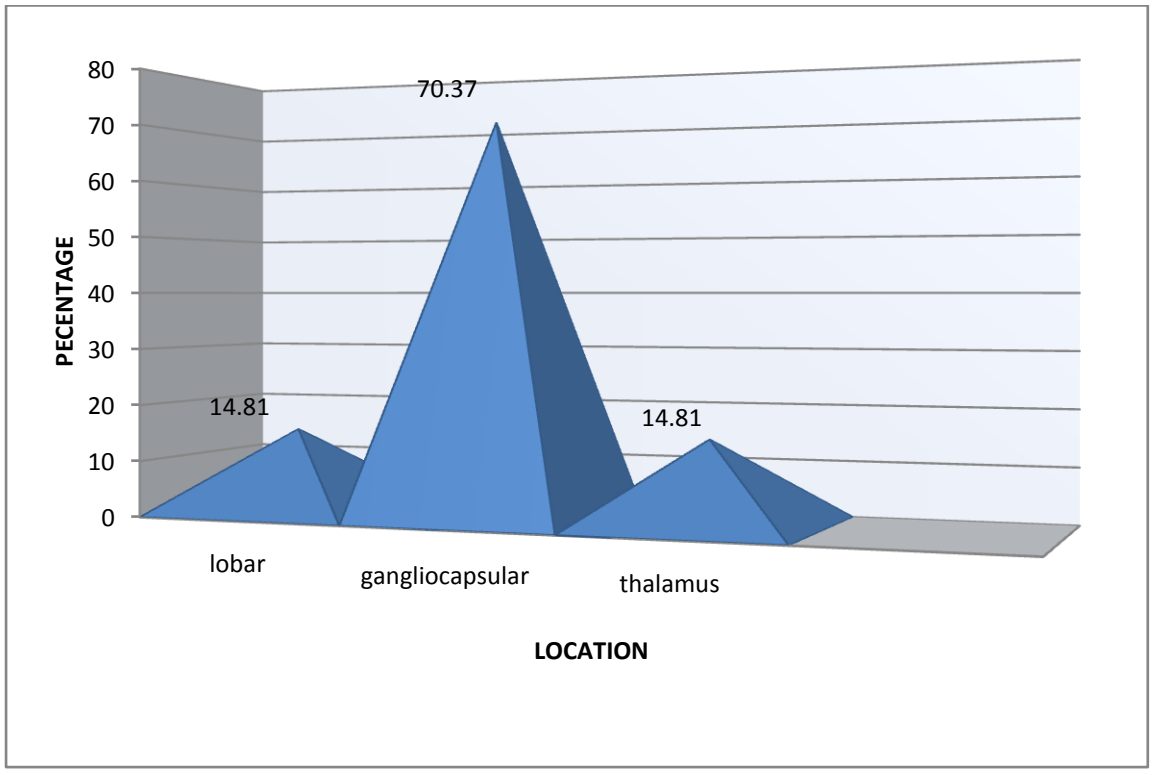

Chart. 20. location of hematoma among poor prognostic group.

The most common location was gangliocapsular region.

Volume of ICH

Volume (ml)	Frequency	Percentage
< 30	3	11.11
31 – 60	14	51.85
61 – 90	7	25.92
91 – 120	2	7.40
>120	1	3.70

Table 21. volume of hematoma in poor prognostic group.

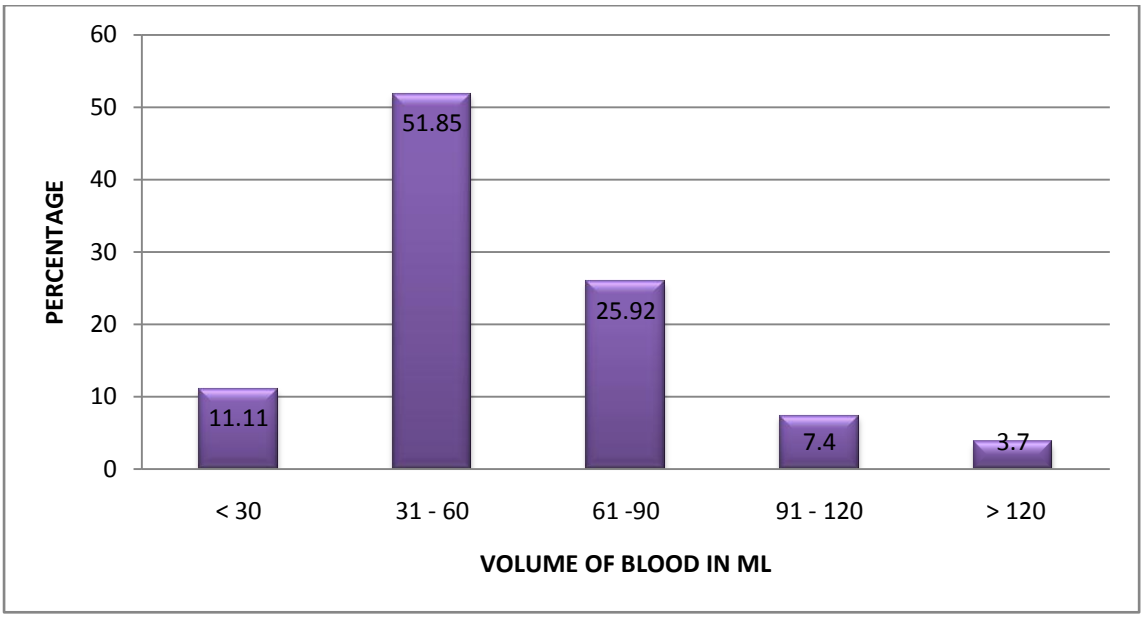

Chart.21. volume of hematoma in poor prognostic group.

The mean volume of hematoma in this group was 59.48 ml (SD 25. 97) , and it is statistically significant ($P < 0.05$) .

Serum ferritin values

Sr.ferritin (ng/ml)	Frequency	Percentage
< 200	7	25.92
200 – 300	15	55.55
300 – 400	1	3.70
>400	4	14.81

Table 22. serum ferritin values in poor prognostic group.

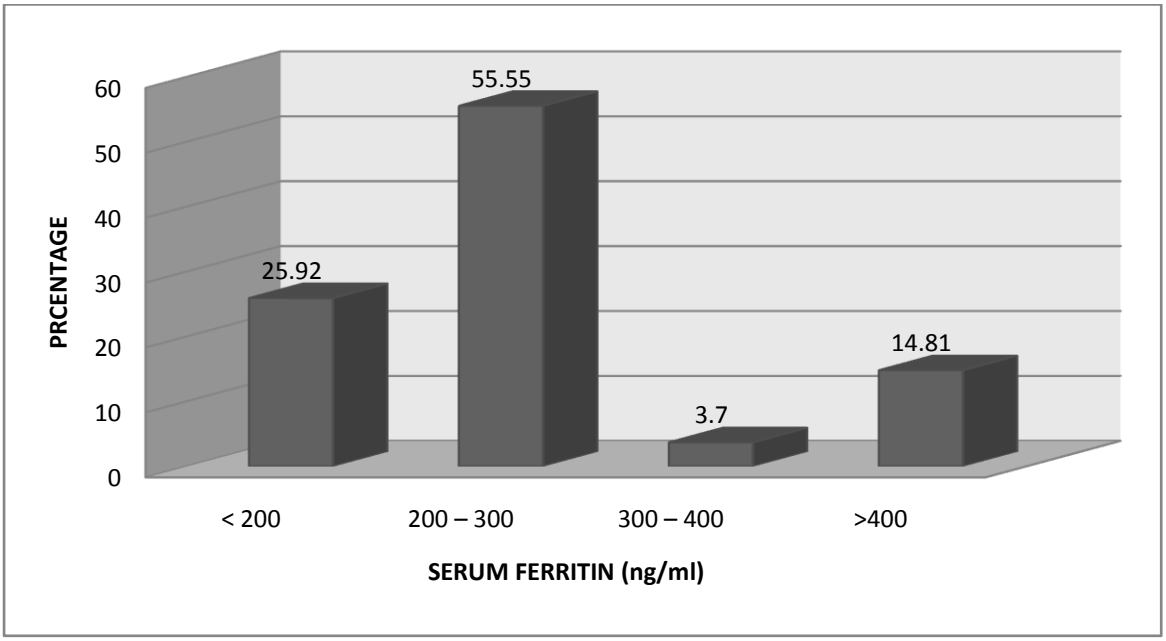

Chart.22. serum ferritin values in poor prognostic group.

Fifty five percentage of patients had their serum ferritin values in the range of 200 – 300 ng/ml. Four patients had their serum ferritn value more than 400 ng / ml. The mean serum ferritin value was 265.11 ng/ml (SD 84.04). This difference is statistically significant ($P < 0.05$).

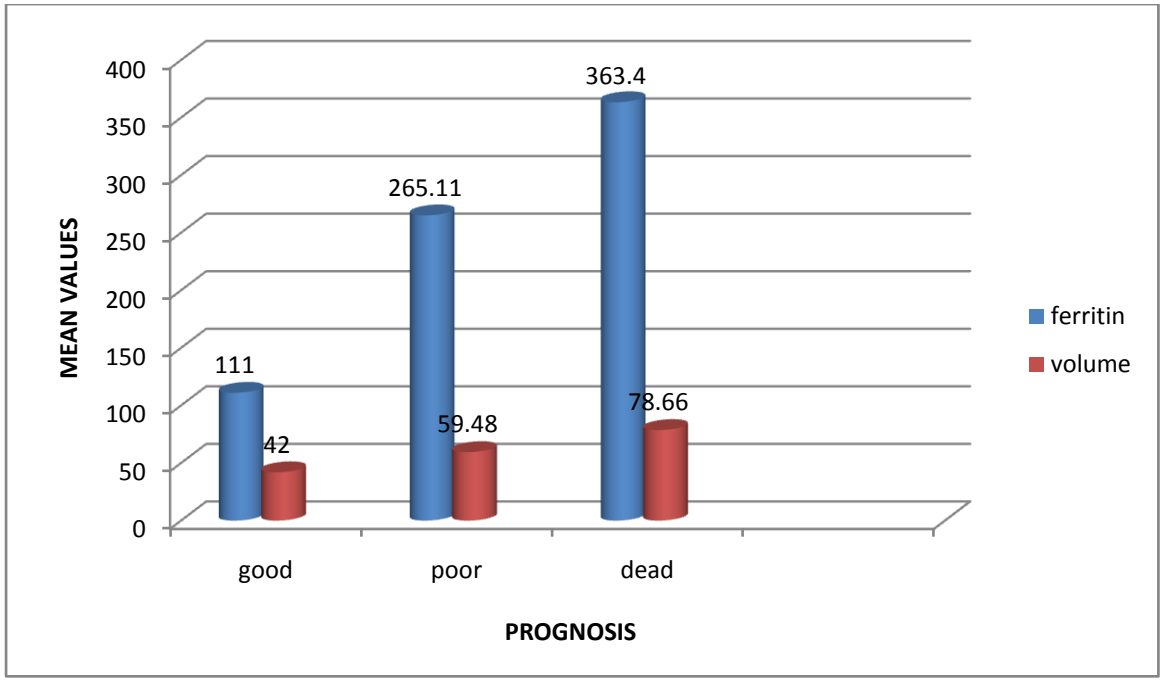

Chart 23.comparison of volume and serum ferritin levels in various groups.

In general,

Mean volume of ICH==78.66ml.

Mean value of ferritin==363.40 ng/ml

In good prognostic group,

Mean volume of ICH = 24.12 ml

Mean value of sr ferritin = 111 ng/ml.

In bad prognostic group,

Mean volume of ICH = 59.48 ml

Mean ferritin value = 265.11 ng/ml.

In mortality group,

Mean volume of ICH = 78.66 ml.

Mean ferritin value= 363.40 ng/ml.

Group	frequency	Mean	S.Deviation	Median
Good prognosis	8	12.125	0.9910	12.000

(column A)				
Bad prognosis (column B)	27	8.519	1.626	8.000
mortality (column C)	15	5.533	1.727	5.000

Table 24. comparison of GCS among different prognostic groups.

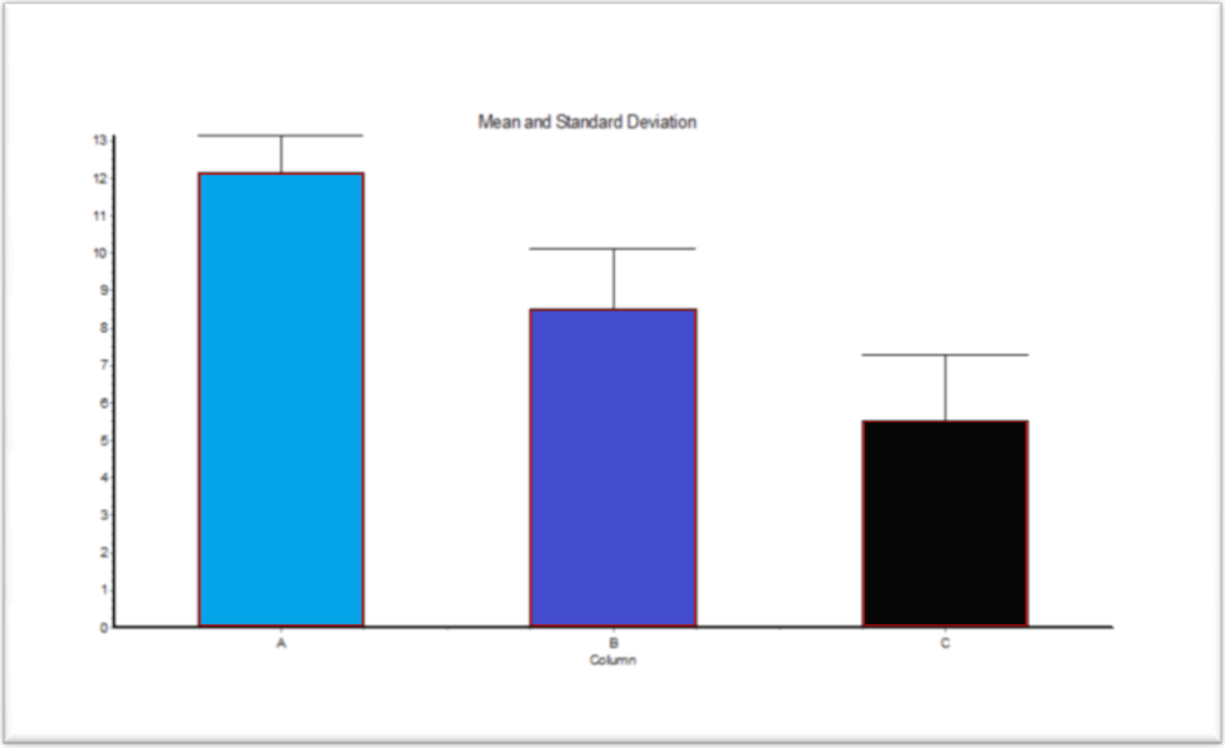

Chart. 24. Comparison of GCS among different prognostic groups

(P < 0.001) CI 95%.

On comparing, the difference in admitting GCS between different prognostic groups is statistically significant with P < 0.001 and confidence interval of 95%.

Group	Points	Mean	S.Deviation	Median
Good prognosis (Column A)	8	24.125	8.391	24.000
Poor prognosis (Column B)	27	59.481	25.972	56.000
Mortality (Column C)	15	78.667	23.295	80.000

Table 25. Comparison of volume of hematoma in different prognostic groups.

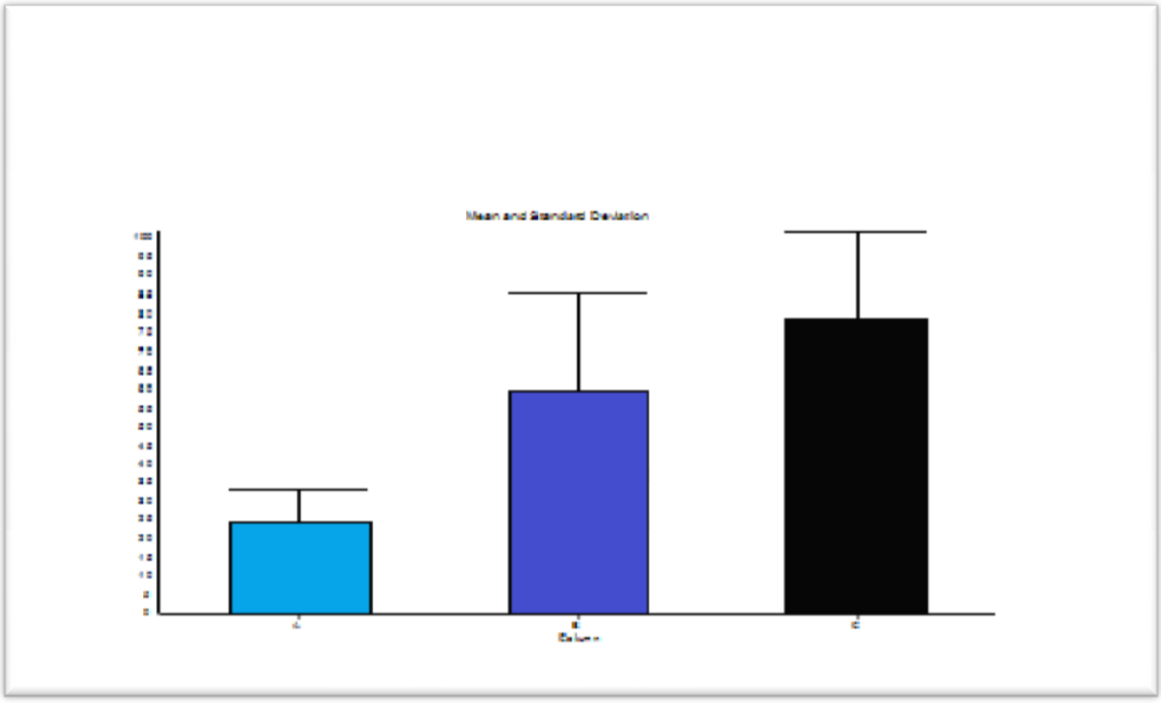

Chart 25. Comparison of volume of hematoma in different prognostic groups. (P < 0.05). CI 95%.

On comparing, the hematoma volume between different prognostic groups is statistically significant with P< 0.05 and CI 95%.

Group	Points	Mean	S.Deviation	Median
Column A	8	111.00	32.018	121.00
Column B	27	265.11	84.045	260.00
Column C	15	363.40	46.176	372.00

Table 26. comparison of serum ferritin values among different prognostic groups.

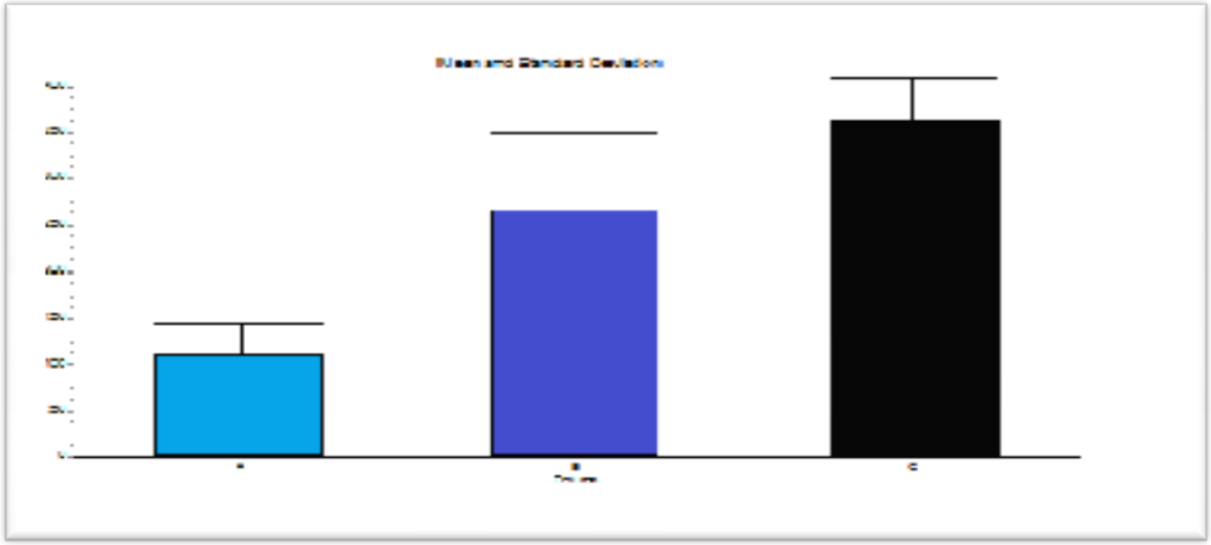

Chart. 26. comparison of serum ferritin values among different prognostic groups (P<.05, CI 95%)

On comparing , there is statistically significant difference of serum ferritin levels between different prognostic groups.

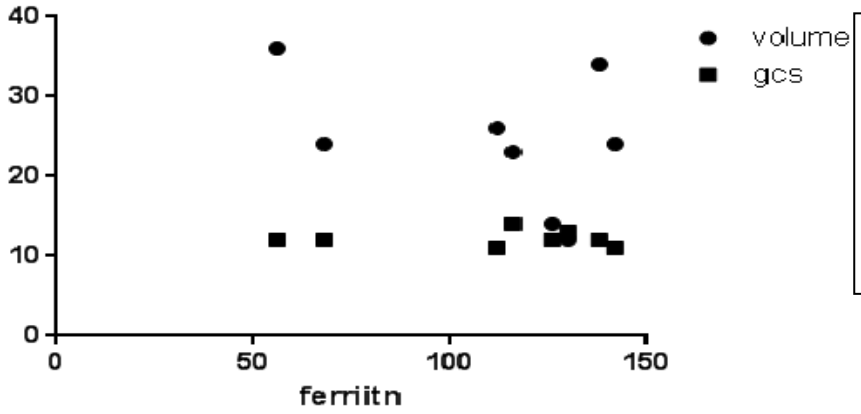

Chart 27.corelation between volume ,GCS and ferritin in good prognostic group.

The two-tailed P value is 0.4646, considered not significant.

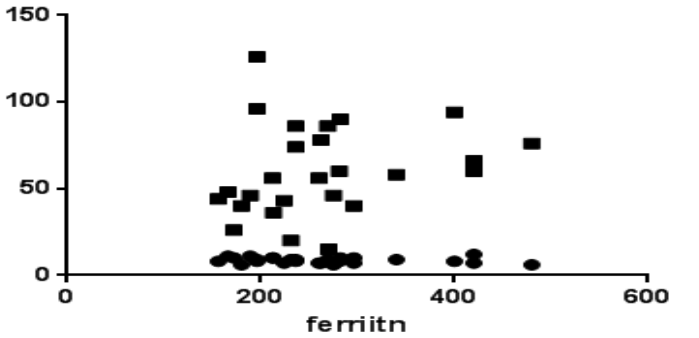

Chart 28.corelation between volume ,GCS and ferritin in poor prognostic group.

The two-tailed P value is 0.5597, considered not significant

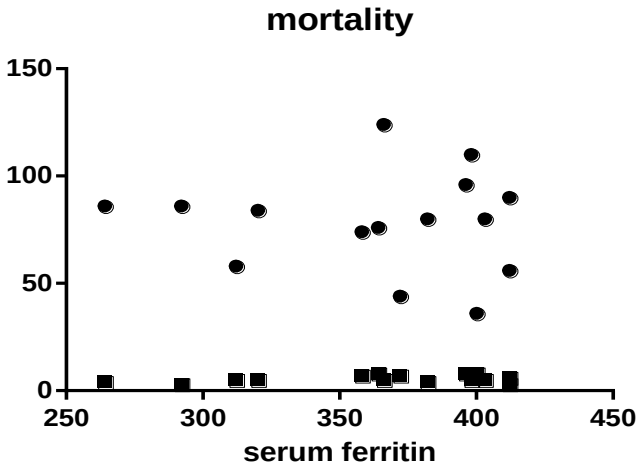

Chart 29.corelation between volume ,GCS and ferritin in poor prognostic group.

The two-tailed P value is 0.9551, considered not significant

There is no correlation between volume ,GCS and serum ferritin in different prognostic groups.

DISCUSSION

This study was conducted on 50 patients with acute intracerebral hemorrhage to find out the serum ferritin levels and correlation between different prognostic groups.

In the previous studies by William Whitely et al (128),the other variables that are associated with poor outcome include , body temperature, blood glucose, C-RP, WBC , serum cortisol , elevated plasma and CSF levels of glutamate, glycine and IL-6.

It is likely that the inflammatory response is triggered by stroke process and mediated by IL-1 (fever) and IL-6 / TNF with rise in acute phase reactants such as C-RP etc that may enhance neurotoxicity. However the initial rise in serum ferritin levels at the onset of stroke is not associated with inflammatory response and correlate with the body iron stores. In the study by Natalia Perez et al , it has been proved that the serum ferritin levels are not correlated with other markers of inflammatory response (49). It is again confirmed by Armengolu et al.(50).

Antonio Davlos et al has also proved association between increased body iron stores as measured by serum ferritin and clinical detoriation of acute cerebral infarction.

The beneficial effect of iron chelation by deferoxamine has been proved in experimental animals by independent investigator ; Masanobu et.al. in rats (118) and Yuxiang gu in piglets (119). No adverse effects was found out in humans with desferoxamine infusion by Magdy selim (120). So if the role of Iron in ICH is proved by many studies with large sample size , the role of iron chelation can be studied in future.

In this current study of 50 patients with primary supratentorial hemorrhage admitted in our hospital , the incidence of ICH is high among the age group of 51 – 70 years. The mean age of onset of ICH reported by Natalia Perez was 66 years.

Males are more commonly affected 4 times higher than females (4:1). Hypertension is the most commonly associated risk factor (98%) in this study population. It is similar to the other study series and is the most common cause of ICH worldwide as reported by Caplan and Kase (69). Diabetes mellitus is present in 18 % of the study population.

The most common location of hypertensive ICH is lateral gangliocapsular region. In a clinico pathological series by Cole and Yates, it has been found that the microaneurysms caused by hypertension were commonly located in this region (70). In our study, the most common location of ICH is gangliocapsular region followed by lobar and thalamus. Older patients are having little higher incidence of lobar hemorrhage located in temperoparietal region. The cerebral

amyloid angiopathy as a cause of lobar hemorrhage in older age group cannot be ruled out in the absence of follow up and histopathalogical correlation.

Headache is the second most common symptom after focal neurological deficit. It is present in 50% of the study population. It is in contrast to other series in which headache is present in only in 40 %.

The overall mortality is 30 % in this study population. This is also higher than the reported mortality rate of 10 – 20 % among developed countries. In part it can be explained by lack of long term care facilities in most part of India and associated complications of immobilization. The average mortality rate reported by Das et.al is 18 -41 % in India (9, 10).

The high mortality occurs in age group of 51 – 70 years in this study population (66.66 %). Ten out of thirty patients in this age group died due to ICH.

The serum ferritin levels are significantly elevated among the bad prognostic group with Modified Rankin Score of more than 2. The mean serum ferritin value is 111 ng/ml (SD 32.018). The mean ferritin values are 265.11 ng/ml (SD 84.04) and 363.40 ng /ml in patients with MRS 3 to 5 and 6 respectively. The difference is statistically significant ($p < 0.05$). Hence the serum ferritin level at the baseline can be used as a prognostic marker in ICH. This is similar to the results obtained by Natalie et.al in his study. The mean ferritin value in that study was 270.6 ng/ml in bad prognostic group (49).

Among other prognostic factors, GCS and volume of ICH are positively correlated with the prognosis. The mean GCS in study population with MRS < 2 , 3-5 and 6 are 12 (SD 0.09), 8 (SD 1.6) and 5.5 (SD 1.7) respectively. The difference is statistically significant with P< 0.05. The correlation between GCS has been proved by Kase and Crowell (60).

The volume of ICH is another independent predictor of prognosis (108). In our current study the mean volume of ICH are 24 ml (SD 8.3) , 59.48 ml (SD 25.97) and 78.66 ml (SD 23.29) among the patients with MRS < 2 , 3-5 and 6 respectively. This observation is statistically significant (P < 0.05).

Manu Mehriditta found no significant correlation between the serum ferritin levels and the volume of ICH (46). In our study ,the serum ferritin values have no significant correlation either with admitting GCS and volume of hematoma in all prognostic groups (tailed P value >0.05). Hence the serum ferritin values are independent of other markers of prognosis.

CONCLUSION

In our study of 50 patients with primary supratentorial intracerebral hemorrhage ,

1. The baseline serum ferritin can be used as an independent prognostic marker.
2. The serum ferritin levels are not influenced by the volume of ICH and admitting GCS.
3. The increased body iron stores as measured by ferritin is associated with clinical detoriation.
4. The hypertension is the most common risk factor associated with ICH.
5. The most common site of bleed is gangliocapsular region.
6. The absence of diabetes, younger age and absence of IVH and midline shift are associated with good prognosis.
7. The presence of low GCS is associated with poor prognosis.
8. The higher the volume of hematoma, poorer the prognosis.
9. The initial volume of hematoma as measured by ABC/2 is accurate in predicting prognosis.

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ABBREVATIONS

AVM	Arteriovenous malformation
CRP	Complement reactive protein.
CSF	Cerebro spinal fluid.
CAA	Cerebral amyloid angiopathy.
CTA	CT-angiography.
DALY	Disablity adjusted life years.
DFX	Deferoxamine.
EPO	Erythropoietin
GCS	Glasgow coma scale.
H-CHAIN	Heavy chain.
ICH	Intracerebral hemorrhage.
IVH	Intraventricular hemorrhage.
LSD	Lysergic acid diethyamide.
LOC	Loss of consciousness.
L-CHAIN	Light chain.
LDL	Low density lipoprotein.
Mcg	Microgram.
NPBI	Non protein bound iron.
PPA	Phenyl propanolamine.
PCP	Phencyclidine.
SHIP	Study of health in Pomerania.
Sr	Serum
STICH	Surgical treatment for intracarebral hemorrhage .

PROFORMA.

EVALUATION OF SERUM FERRRITN LEVELS AS A PROGNOSTIC MARKER IN ACUTE HEMORHAGIC STROKE.

- ***NAME :*** ***AGE:***
- ***SEX:***
- ***ADDRESS:*** ***I.P.NO:***

- ***PAST HISTORY:***
  - ***CVA. CHD. CKD. SHT. DM. CLD.***
  - ***Hemophilia. Leukemia. Rheumatoid arthritis.***
- ***DRUG HISTORY:***
  - ***Antiplatlets. Anticoagulants.***
  - ***Others.***
- ***PERSONAL HISTORY:***
  - ***Smoking. Alcohol.***
  - ***Narcotics .***

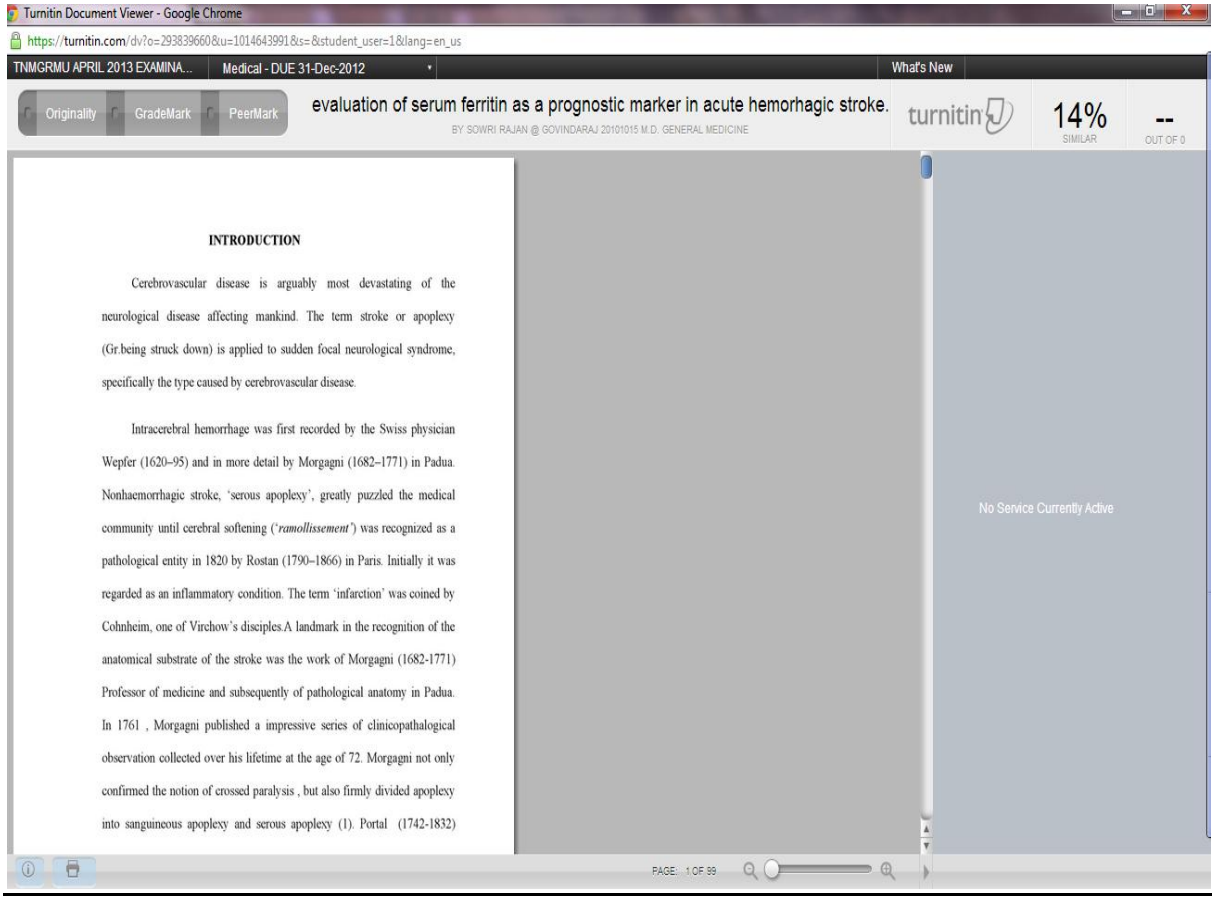
- ***CLINCAL FEATURES:***
  - ***Symptoms:*** ***Headache.***
    - ***Vomiting.***
    - ***Convulsions.***
    - ***Diplopia.***
    - ***Blurring of vision.***
    - ***Trauma.***
  - ***Signs:***
    - ***Vitals***
      - ***PR:*** ***BP:*** ***RR:*** ***GCS:***
      - ***TEMP***
    - ***cranial nerves.***
    - ***Pupils***
    - ***Motor weakness.***
    - ***Sensory abnormalities.***
    - ***Bladder and bowel.***
    - ***Involuntary mvt.***
    - ***Papiledema***

- ***OTHER SYSTEMS :***
    - ***CVS;*** ***RS;*** ***ABD;***
    - ***SK.DEFORMITIES;***
- ***INVESTIGATIONS:***
    - ***CBC:*** ***RFT:*** ***eGFR: LFT:***
    - ***Peripheral smear:***
    - ***USG abodomen:***
    - ***CT BRAIN:***
        - ***Location.*** ***Volume.***
        - ***Midline shift.*** ***IVH.***

- ***Serum ferritin.***

- ***GCS:***

- ***Modified Rankin score:***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evaluation of serum ferritin as a prognostic marker in acute hemorhagic stroke.
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INTRODUCTION
Cerebrovascular disease is arguably most devastating of the neurological disease affecting mankind. The term stroke or apoplexy (Gr.being struck down) is applied to sudden focal neurological syndrome, specifically the type caused by cerebrovascular disease.
Intracerebral hemorrhage was first recorded by the Swiss physician Wepfer (1620–95) and in more detail by Morgagni (1682–1771) in Padua. Nonhaemorrhagic stroke, 'serous apoplexy', greatly puzzled the medical community until cerebral softening (*'ramollissement'*) was recognized as a pathological entity in 1820 by Rostan (1790–1866) in Paris. Initially it was regarded as an inflammatory condition. The term 'infarction' was coined by Cohnheim, one of Virchow's disciples.A landmark in the recognition of the anatomical substrate of the stroke was the work of Morgagni (1682-1771) Professor of medicine and subsequently of pathological anatomy in Padua. In 1761 , Morgagni published a impressive series of clinicopathalogical observation collected over his lifetime at the age of 72. Morgagni not only confirmed the notion of crossed paralysis , but also firmly divided apoplexy into sanguineous apoplexy and serous apoplexy (1). Portal (1742-1832)
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INTRODUCTION Cerebrovascular disease is arguably most devastating of the neurological disease affecting mankind. The term stroke or apoplexy (Gr.being struck down) is applied to sudden focal neurological syndrome, specifically the type caused by cerebrovascular disease. Intracerebral hemorrhage was first recorded by the Swiss physician Wepfer (1620–95) and in more detail by Morgagni (1682–1771) in Padua. Nonhaemorrhagic stroke, 'serous apoplexy', greatly puzzled the medical community until cerebral softening ('ramollissement') was recognized as a pathological entity in 1820 by Rostan (1790–1866) in Paris. Initially it was regarded as an inflammatory condition. The term 'infarction' was...

S.NO	NAME	AGE	HOSPITAL NO:	PRESENTING COMPLAINTS					RISK FACTORS		CLINICAL EXAMINATION								INVESTIGATIONS					OUTCOME	
																			NECT BRAIN						
				HEADACHE	VOMITING	FOCAL DEFICIT	LOC	SEIZURES	HYPERTENTION	DIABETES	PULSE	B.P	R.R	CVS	RS	CNS	FUNDUS	GCS (x/15)	LOCATION	VOLUME	MIDLINE SHIFT	IVH	Sr.FERRITIN	MRS -7TH DAY	MRS-30TH DAY
1.	Boss	64/M	61513	-	-	+	-	-	+	-	68	170/100	12	N	N	LHP	N	12	R.GC	60	-	+	420	5	5
2.	Indhrani	65/F	63007	+	-	+	+	-	+	-	96	180/96	14	N	N	RHP	N	4	LTP	86	+	+	264	6	-
3.	Nallusamy	66/M	65463	-	-	+	-	-	+	+	66	200/100	15	N	N	LHP	N	3	RGC	90	-	-	412	6	-
4.	Kannan	72/M	65484	-	-	+	-	-	+	-	74	170/100	14	N	N	LHP	N	7	RGC	40	-	-	296	5	4
5.	Mariyadass	30/M	65998	+	+	+	-	+	+	-	69	180/108	13	N	N	LHP	N	10	RGC	36	-	-	213	3	3
6.	Kamatchi	33/F	67034	+	+	+	-	-	+	-	84	160/96	16	N	N	RHP	N	11	LGC	24	-	-	142	2	2
7.	Ravindran	50/M	68008	-	-	+	-	-	+	-	72	156/100	12	N	N	RHP	N	9	LGC	74	-	-	236	5	4
8.	Babu	65/M	70404	-	+	-	-	-	+	+	80	172/112	13	N	N	LHP	N	7	R.THAL	66	-	-	420	5	5
9.	Samuvel	49/M	70497	-	-	+	-	-	+	-	63	148/94	14	N	N	RHP	N	6	LGC	40	-	-	180	4	3
10.	Chakkubai	46/M	71228	+	-	+	+	-	+	+	99	154/92	16	N	N	LHP	N	7	RGC	78	-	+	262	5	4

11.	Krishnan	36/M	71268	+	-	+	-	+	+	-	78	146 80	13	N	N	LHP	N	13	RGC	12	-	-	130	2	2
12.	Karunakaran	55/M	73160	-	-	+	-	-	+	-	66	156 100	12	N	N	LHP	N	11	RGC	46	-	-	189	3	3
13.	Thangaraj	70/M	74834	-	+	+	-	+	+	+	60	164 110	13	N	N	RHP	N	5	LTP	80	-	-	403	6	-
14.	Anandhan	80/M	75151	-	-	+	-	-	+	-	83	172 98	14	N	N	RHP	N	3	LGC	86	-	-	292	6	-
15.	Rajan	64/M	76051	-	-	+	-	-	+	-	70	148 90	12	N	N	LHP	N	12	R THAL	34	-	-	138	2	2
16.	Pandaram	65/M	77514	-	-	+	+	-	+	-	84	178 100	14	N	N	LHP	N	8	RGC	94	-	-	400	5	5
17.	Jacob	57/M	80783	+	-	+	-	-	+	-	60	152 94	12	N	N	RHP	N	9	L THAL	20	-	-	231	4	4
18.	Balan	58/M	80825	+	+	+	-	-	+	-	76	182 100	16	N	N	RHP	N	7	LGC	44	-	+	372	6	-
19.	Rajeswari	85/F	81245	-	-	+	+	-	+	+	66	140 90	13	N	N	RHP	N	10	LTP	26	-	-	172	4	4
20.	Samundeeswari	55/F	83787	+	+	+	-	+	+	-	56	166 98	15	N	N	RHP	N	5	LGC	58	-	+	312	5	6
21.	Gowridevi	43/F	83866	+	+	+	-	-	+	-	77	158 98	12	N	N	RHP	N	10	LGC	90	-	-	282	5	4
22.	Indhrani	70/F	86078	-	-	+	-	-	+	-	98	146 100	16	N	N	RHP	N	11	L THAL	48	-	-	166	3	3
23.	Raj	54/M	87555	+	-	+	-	-	+	-	65	170 98	15	N	N	LHP	N	14	RGC	23	-	-	116	2	1
24.	Jonadoss	40/M	87794	+	+	+	+	-	+	-	78	196 110	12	N	N	RHP	N	5	LGC	110	-	-	398	5	6
25.	Iyyappan	55/M	88068	-	-	+	-	-	+	+	84	164 96	12	N	N	LHP	N	5	RTP	124	-	-	366	6	-
26.	Raghunandhdan	43/M	89638	+	+	+	-	-	+	-	56	148 74	15	N	N	LHP	N	9	RGC	86	-	-	269	4	4
27.	Kathirvel	60/M	90717	-	-	+	-	-	+	-	72	150 90	12	N	N	RHP	N	8	L THAL	76	-	+	364	6	-

28.	Janaki	70/F	90724	-	-	+	-	-	+	+	66	148 78	11	N	N	RHP	N	10	LGC	40	-	-	296	5	5
29.	Prabakar rao	40/M	92628	-	-	+	-	-	+	-	72	176 96	13	N	N	LHP	N	4	R THAL	80	-	+	382	5	6
30.	Ravi	35/F	94256	+	-	+	+	-	-	-	68	138 98	12	N	N	LHP	N	12	LGC	14	-	-	126	2	1
31.	Patchiappan	70/M	96471	-	-	+	-	-	+	-	87	156 94	14	N	N	LHP	N	8	RGC	44	-	-	156	3	3
32.	Krishnan	80/M	96788	-	-	+	-	-	+	+	68	180 94	11	N	N	RHP	N	8	LTP	36	-	+	400	5	6
33.	Gubendran	65/M	97135	-	-	+	-	-	+	-	56	176 76	12	N	1I	RHP	N	9	LGC	58	-	-	340	5	4
34.	Murali	56/M	97469	+	-	+	-	-	+	-	67	180 108	16	N	N	LHP	N	12	RGC	36	-	-	56	2	1
35.	Kumar	52/M	97583	-	-	+	-	-	+	+	78	156 98	14	N	N	RHP	N	9	LTP	126	-	-	196	5	4
36.	Kanim	55/M	98152	+	-	+	-	-	+	-	89	148 112	13	N	N	LHP	N	8	RTP	86	-	+	236	4	4
37.	Thangaraj	60/M	98207	-	-	+	+	-	+	-	66	156 78	12	N	N	LHP	N	7	RGC	74	-	-	358	5	6
38.	Arumugam	45/M	99548	+	-	+	+	-	+	-	79	180 98	12	N	N	RHP	N	8	LGC	96	-	+	196	5	4
39.	Dhandapani	52/M	99603	+	-	+	-	-	+	-	64	146 76	15	N	N	RHP	N	7	LGC	43	-	-	224	4	4
40.	Ramakrishnan	53/M	99739	+	+	+	-	-	+	-	56	180 110	12	N	N	RHP	N	6	LGC	76	-	-	480	5	5
41.	Bhgavan	45/M	100070	-	-	+	-	-	+	-	66	178 90	13	N	N	LHP	N	12	RGC	24	-	-	68	2	1
42.	Rajamanickam	56/M	100114	+	+	+	+	-	+	-	70	176 100	12	N	N	RHP	N	6	LGC	56	-	+	412	5	6
43.	Usman	68/M	100311	-	-	+	-	-	+	-	65	178 98	13	N	N	RHP	N	5	LGC	84	-	-	320	6	-
44.	Ibrahimbai	45/M	101684	+	+	+	-	-	+	-	76	168 96	12	N	N	RHP	N	8	LGC	60	-	-	281	4	4
45.	Mohan rao	55/M	102462	+	-	+	-	+	+	-	66	148	11	N	N	LHP	N	8	R PAR	15	-	-	270	5	4

												96												
46.	Nirmala	65/F	102831	+	+	+	+	-	+	-	60	178/90	14	N	N	RHP	N	7	L THAL	56	-	-	260	4	4
47.	Lakshmi	56/F	102914	-	-	+	-	-	+	-	61	148/94	12	N	N	LHP	N	8	RGC	96	-	+	396	6	-
48.	Ramayee	45/F	103599	+	+	+	-	-	+	-	72	154/94	11	N	N	RHP	N	6	LGC	46	-	-	275	5	5
49.	Suresh	36/M	103602	+	+	+	-	-	+	-	54	178/100	10	N	N	LHP	N	11	RGC	26	-	-	112	2	2
50.	muthulingam	57/M	103612	+	-	-	-	-	+	-	74	180/98	12	N	N	LHP	N	10	RGC	56	-	-	212	3	3

KEY TO MASTER CHART.

B.P	Blood pressure.
C.V.S	Cardiovascular system.
C.N.S	Central nervous system.
F	Female.
G.C.S	Glassgow coma scale.
I.V.H	Intraventricular hemorrhage.
L.O.C	Loss of consciousness.
L.G.C	Left gangliocapsular region.
L.T.P	Left temperoparietal region.
L.THAL	Left thalamus.
M	Male.
M.R.S	Modified Rankin scale.
R.S	Respiratory system.
R.R	Respiratory rate.
R.T.P	Right tempero parietal region.
R.G.C	Right ganglio capsular region.
R.THAL	Right thalamus.
+	Present.
-	Absent.

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI -3

Telephone No : 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. R.Sowrirajan @ Govindaraj
PG in MD General Medicine
Madras Medical College, Chennai -3

Dear Dr. R.Sowrirajan @ Govindaraj

The Institutional Ethics committee of Madras Medical College, reviewed and discussed your application for approval of the proposal entitled "Evaluation of serum ferritin levels as a prognostic marker in acute hemorhagic stroke" No.15062012.

The following members of Ethics Committee were present in the meeting held on 19.06.2012 conducted at Madras Medical College, Chennai -3.

1. Dr. S.K. Rajan. M.D.,FRCP.,DSc -- Chairperson
2. Prof. K. Ramadevi MD -- Member
   Prof of Biochemistry, MMC, Ch-3
3. Prof. R. Nandhini MD -- Member
   Director, Inst. of Pharmacology ,MMC, Ch-3
4. Prof. C. Rajendiran, MD -- Member
   Director , Inst. of Internal Medicine, MMC, Ch-3
5. Prof. S. Deivanayagam MS -- Member
   Prof of Surgery, MMC, Ch-3
6. Prof. A. Radhakrishnan MD
   Prof of Internal Medicine, MMC, Ch-3

We approve the proposal to be conducted in its presented form.

Sd/ Chairman & Other Members

The Institutional Ethics Committee expects to be informed about the progress of the study, and SAE occurring in the course of the study, any changes in the protocol and patients information / informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee